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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09   CA/CAplus records now contain indexing from 1907 to the
                   present
 NEWS  4  DEC 08   INPADOC: Legal Status data reloaded
 NEWS  5  SEP 29   DISSABS now available on STN
 NEWS  6  OCT 10   PCTFULL: Two new display fields added
 NEWS  7  OCT 21   BIOSIS file reloaded and enhanced
 NEWS  8  OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9  NOV 24   MSDS-CCOHS file reloaded
 NEWS 10  DEC 08   CABA reloaded with left truncation
 NEWS 11  DEC 08   IMS file names changed
 NEWS 12  DEC 09   Experimental property data collected by CAS now available
                   in REGISTRY
 NEWS 13  DEC 09   STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14  DEC 17   DGENE: Two new display fields added
 NEWS 15  DEC 18   BIOTECHNO no longer updated
 NEWS 16  DEC 19   CROPU no longer updated; subscriber discount no longer
                   available
 NEWS 17  DEC 22   Additional INPI reactions and pre-1907 documents added to CAS
                   databases
 NEWS 18  DEC 22   IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19  DEC 22   ABI-INFORM now available on STN
 NEWS 20  JAN 27   Source of Registration (SR) information in REGISTRY updated
                   and searchable
 NEWS 21  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS 22  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS 23  MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS 24  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS 25  MAR 03   FRANCEPAT now available on STN

 NEWS EXPRESS  DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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 NEWS LOGIN    Welcome Banner and News Items
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  * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004

=> e marchalonis john j/in
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
The EXPAND command is used to look at the index in a file
which has an index.  This file does not have an index.

=> file uspatful
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY     SESSION
FULL ESTIMATED COST                                        0.21        0.21

FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Mar 2004 (20040304/PD)
FILE LAST UPDATED: 4 Mar 2004 (20040304/ED)
HIGHEST GRANTED PATENT NUMBER: US6701528
HIGHEST APPLICATION PUBLICATION NUMBER: US2004045070
CA INDEXING IS CURRENT THROUGH 4 Mar 2004 (20040304/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Mar 2004 (20040304/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
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>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> e marchalonis john j/in
E1            2     MARCHAL STEPHANIE/IN
E2            2     MARCHAL XAVIER/IN
E3            2 --> MARCHALONIS JOHN J/IN
E4            2     MARCHALOT GABRIEL/IN
E5            2     MARCHALOT JEAN NOEL/IN
E6            1     MARCHAM DOUGLAS H/IN
E7            1     MARCHAM JAMES SYDNEY/IN
E8            1     MARCHAND AGNES/IN
E9            4     MARCHAND ALAIN/IN
E10           1     MARCHAND ALAIN C S/IN
E11           2     MARCHAND ALAIN LE/IN
E12           1     MARCHAND ALAIN R/IN

=> s e3
L1            2 "MARCHALONIS JOHN J"/IN

=> d l1,cbib,ab,clm,1-2

L1   ANSWER 1 OF 2  USPATFULL on STN
1999:67011 T-cell receptor peptides and methods for preventing the progression
    to AIDS in an animal model.
    Marchalonis, John J., Tucson, AZ, United States
    Watson, Ronald R., Tucson, AZ, United States
    Dehghanpisheh, Keivan, Portland, OR, United States
    Wang, Yuejian, St. Paul, MN, United States
    Huang, Dennis S., Shaker Heights, OH, United States
```

Arizona Board of Regents on Behalf of the University of Arizona, Tucson, AZ, United States (U.S. corporation)
US 5911990 19990615
APPLICATION: US 1996-696049 19960813 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel peptide from the T-cell receptor is shown to be effective in preventing the progression to AIDS in an animal model. Methods for delaying the progression to AIDS and restoring normal immunological responses in an animal model following infection are shown and comprise administering through various systemic routes T-cell receptor peptide Vβ CDR1 to restore normal levels of Th1 cytokines interleukin 2 and interferon-γ, which are suppressed following infection, and those of Th2 derived cytokines interleukin 5, interleukin 6, interleukin 10, and immunoglobulin G, which are stimulated following infection.
CLM What is claimed is:
1. A method of modulating the immune response in a mammal infected with a C-type retrovirus or a lentivirus, comprising administering by a systemic route an amount of T-cell receptor Vβ CDR1 peptide of SEQ ID NO:1 sufficient to stimulate the production of interleukin 2 and interferon-γ, and to suppress the production of interleukin 5, interleukin 6, interleukin 10, and immunoglobulin G.

2. The method of claim 1, wherein said lentivirus comprises HIV.

3. A method of altering the immune system response of a host infected with a C-type retrovirus or a lentivirus, comprising artificially introducing a T-cell receptor Vβ CDR1 peptide of SEQ ID NO: 1 into the bloodstream or immune system by injection so as to artificially induce said immune system to stimulate production of Th1 cytokines or suppress production of Th2 derived cytokines.

4. The method of claim 3, wherein said lentivirus comprises HIV.

5. The method of claim 3, wherein said lentivirus comprises feline immunodeficiency virus.

6. A method of altering the immune system response of a host suffering from an infectious disease comprising artificially introducing a T-cell receptor Vβ CDR1 peptide of SEQ ID NO: 1 into the bloodstream or immune system by injection so as to artificially induce said immune system to stimulate production of Th1 cytokines or suppress production of Th2 derived cytokines.

L1 ANSWER 2 OF 2 USPATFULL on STN
92:86950 Synthetic senescent cell antigen.
Kay, Marguerite M. B., Temple, TX, United States
Marchalonis, John J., Tucson, AZ, United States
Research Corporation Tech., Inc., Tucson, AZ, United States (U.S. corporation)
US 5157020 19921020
APPLICATION: US 1990-528210 19900524 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein is a synthetic senescent cell antigen comprised of purified peptides immunoreactive with antibodies to the naturally occurring antigen. Preferably, the synthetic senescent cell antigen comprises two peptides with the amino acid sequences SKLIKIFQDHPLQKTYN and LFKPPKYHPDVPYVKR, respectively. The antigen and peptides may be used in compositions, diagnostic kits, and methods for detecting or measuring antibodies to senescent cell antigen, studying cellular aging and autoimmune mechanisms, separating anions from a gas or liquid, or treating certain diseases.
CLM What is claimed is:

1. A peptide consisting essentially of a molecule of up to 15 amino acids linked by peptide bonds wherein said peptide is immunoreactive with antibodies to senescent cell antigen.

2. The peptide of claim 1 wherein said peptide is encoded by the nucleotide sequences 1612 to 1662 as shown in FIG. 1.

3. The peptide of claim 1 wherein said peptide is encoded by the nucleotide sequences 2434 to 2481 as shown in FIG. 1.

4. A peptide consisting essentially of the amino acid sequence SKLIKIFQDHPLQKTYN.

5. A peptide consisting essentially of the amino acid sequence LFKPPKYHPDVPYVKR.

6. A synthetic senescent cell antigen comprising a mixture of a first peptide encoded by the nucleotide sequences 1612 to 1662 as shown in FIG. 1 and a second peptide encoded by the nucleotide sequences 2434 to 2481 as shown in FIG. 1.

7. A synthetic senescent cell antigen comprising a mixture of a first peptide consisting essentially of the amino acid sequence SKLIKIFQDHPLQKTYN and a second peptide consisting essentially of the amino acid sequence LFKPPKYHPDVPYVKR.

8. The synthetic senescent cell antigen of claim 7 wherein said first and second peptides are covalently linked.

9. The synthetic senescent cell antigen of claim wherein each of said peptides is labeled with a detectable moiety.

10. The synthetic senescent cell antigen of claim 7 wherein each of said peptides is bound to an aqueous insoluble material.

11. The synthetic senescent cell antigen of claim 10 wherein said material is a membrane.

12. A pharmaceutical composition comprising a pharmaceutically effective amount of the peptide of claim 1 in a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a pharmaceutically effective amount of the synthetic senescent cell antigen of claim 7 in a pharmaceutically acceptable carrier.

14. The synthetic senescent cell antigen of claim 6 wherein said peptides are covalently linked.

15. The synthetic senescent cell antigen of claim 6 wherein each of said peptides is labeled with a detectable moiety.

16. The synthetic senescent cell antigen of claim 6 wherein each of said peptides is bound to an aqueous insoluble material.

17. The synthetic senescent cell antigen of claim 10 wherein said material is a membrane.

18. The peptide of claim 1 wherein said peptide is labeled with a detectable moiety.

19. The peptide of claim 4 wherein said peptide is labeled with a detectable moiety.

20. The peptide of claim 5 wherein said peptide is labeled with a detectable moiety.

21. The peptide of claim 1 wherein said peptide is bound to an aqueous insoluble material.

22. The peptide of claim 4 wherein said peptide is bound to an aqueous insoluble material.

23. The peptide of claim 5 wherein said peptide is bound to an aqueous insoluble material.

24. A pharmaceutical composition comprising a pharmaceutically effective amount of the peptide of claim 2 in a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a pharmaceutically effective amount of the peptide of claim 3 in a pharmaceutically acceptable carrier.

26. A pharmaceutical composition comprising a pharmaceutically effective amount of the peptide of claim 4 in a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising a pharmaceutically effective amount of the peptide of claim 5 in a pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising a pharmaceutically effective amount of the synthetic senescent cell antigen of claim 6 in a pharmaceutically acceptable carrier.

29. A cosmetic composition comparing a cosmetically effective amount of the peptide of claim 1 in a cosmetically acceptable carrier.

30. A cosmetic composition comprising a cosmetically effective amount of the peptide of claim 2 in a cosmetically acceptable carrier.

31. A cosmetic composition comprising a cosmetically effective amount of the peptide of claim 3 in a cosmetically acceptable carrier.

32. A cosmetic composition comprising a cosmetically effective amount of the peptide of claim 4 in a cosmetically acceptable carrier.

33. A cosmetic composition comprising a cosmetically effective amount of the peptide of claim 5 in a cosmetically acceptable carrier.

34. A cosmetic composition comprising a cosmetically effective amount of the synthetic senescent cell antigen of claim 6 in a cosmetically acceptable carrier.

35. A cosmetic composition comprising a cosmetically effective amount of the synthetic senescent cell antigen of claim 7 in a cosmetically acceptable carrier.

36. The synthetic senescent cell antigen of claim 6 wherein the ratio of said first peptide to said second peptide is 40 to 60 by weight percent.

37. The synthetic senescent cell antigen of claim 7 wherein the ratio of said first peptide to said second peptide is 40 to 60 by weight percent.

=> d l1,exnam

L1 ANSWER 1 OF 2 USPATFULL on STN
EXNAM Primary Examiner: Cunningham, Thomas M.

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=> file wpids
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        15.89      16.10

FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
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FILE LAST UPDATED:          2 MAR 2004      <20040302/UP>
MOST RECENT DERWENT UPDATE:     200415        <200415/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
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>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

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    http://thomsonderwent.com/support/userguides/               <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM
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    SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
    FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<


=> e marchalonis j j/in
E1            1     MARCHALL M D/IN
E2            1     MARCHALONI J J/IN
E3            5 --> MARCHALONIS J J/IN
E4            2     MARCHALOT G/IN
E5            1     MARCHALOT J N/IN
E6            3     MARCHAM A/IN
E7            1     MARCHAM D H/IN
E8           24     MARCHAND A/IN
E9            1     MARCHAND A C S/IN
E10           1     MARCHAND A F T/IN
E11           5     MARCHAND A L/IN
E12           1     MARCHAND A P/IN

=> s e2 or e3
              1 "MARCHALONI J J"/IN
              5 "MARCHALONIS J J"/IN
L2            5 "MARCHALONI J J"/IN OR "MARCHALONIS J J"/IN

=> d l2,ti,1-5

L2   ANSWER 1 OF 5  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New homodimer comprising peptides from a T-cell receptor, useful for
     manufacturing a medicament for modulating or altering an immune response,
     stimulating the production of Th1 cytokines or suppressing production of
     Th2 cytokines.

L2   ANSWER 2 OF 5  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New T-cell receptor-derived peptides for preventing and/or treating human
     immunodeficiency virus infection, cardiovascular diseases and disorders
     and allergic disease.

L2   ANSWER 3 OF 5  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Delaying onset of AIDS in a host infected with an immunodeficiency-type
```

L2 ANSWER 4 OF 5 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Human antibody prepn. enriched for antibodies binding a recombinant human T cell receptor protein - useful to diagnose and treat auto-immune diseases or conditions, e.g. multiple sclerosis or graft versus host disease.

L2 ANSWER 5 OF 5 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Synthetic senescent cell antigen and peptide(s) - used to detect antibodies to SCA, study cellular ageing and auto-immune mechanisms, separate anions and treat auto-immune disease.

=> d l2,bib,ab,1-3

L2 ANSWER 1 OF 5 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 2003-140358 [13] WPIDS
DNC C2003-035580
TI New homodimer comprising peptides from a T-cell receptor, useful for manufacturing a medicament for modulating or altering an immune response, stimulating the production of Th1 cytokines or suppressing production of Th2 cytokines.
DC B04 C06 D16
IN **MARCHALONIS, J J**; WATSON, R R
PA (ARIZ-N) ARIZONA BOARD OF REGENTS; (BASS-I) BASSETT R S
CYC 99
PI WO 2002094860 A2 20021128 (200313)* EN 49p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
EP 1389219 A2 20040218 (200413) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002094860 A2 WO 2002-GB2323 20020517; EP 1389219 A2 EP 2002-730429 20020517, WO 2002-GB2323 20020517
FDT EP 1389219 A2 Based on WO 2002094860
PRAI GB 2001-12126 20010518
AB WO 200294860 A UPAB: 20030224
NOVELTY - A homodimer where each monomer of the homodimer consists of Sequence A, from the N-terminus to the C-terminus direction, where if the sequences are present as an aqueous solution, then 81 % of the occurrences of the sequence are present as a dimer, is new.

DETAILED DESCRIPTION - A new homodimer comprises that each monomer of the homodimer consists of sequence A, from the N-terminus to the C-terminus direction, where if the sequences are present as an aqueous solution, then 81 % of the occurrences of the sequence are present as a dimer.

Cys-Lys-Pro-Ile-Ser-Gly-His-Asn-Ser-Leu-Phe-Trp-Tyr-Arg-Gln-Thr (A)

INDEPENDENT CLAIMS are also included for the following:

(1) a homodimer where each monomer of the homodimer is a homolog of the beta 3 peptide of the T-cell receptor beta chain clone YT35, where the beta 3 peptide consists of Sequence A, and the homolog has the sequence of a segment of another distinct human V beta gene that corresponds to the same segment as the beta 3 peptide;

(2) altering or modulating an immune response in a patient in need of treatment, comprising administering the dimer.

ACTIVITY - Virucide; Antibacterial; Protozoacide; Fungicide; Anti-HIV; Immunosuppressive; Cytostatic; Tuberculostatic; Antiallergic; Cardiant; Antiarthritic; Antirheumatic; Antiarteriosclerotic; Antithyroid; Antidiabetic; Dermatological; Cardiovascular; Nootropic; Neuroleptic.

No biological data is given.

Interleukin-Antagonist-2; Interferon-Antagonist-Gamma;
Interleukin-agonist-5; Interleukin-Agonist-6; Interleukin-Agonist-10.

USE - The new dimer is useful for the manufacture of a medicament for modulating or altering the immune response of an animal, or for stimulating the production of Th1 cytokines and/or suppressing production of Th2 cytokines and/or improving general immune competence. The medicament is also for treating a condition in which auto-antibodies against the family of T-cell receptor (TCR) V beta CDR (complementarity determining regions) peptides are generated, or for preventing or reversing immunosuppression and/or abnormal cytokine production. The medicament is additionally for treating an infectious disease, preferably caused by a virus, or for preventing or reversing the deleterious effects of an immunodeficiency-type retrovirus, where the infectious disease is caused by a C-type retrovirus or a lentivirus. The lentivirus is human immunodeficiency virus (HIV)-1, HIV-2, HIV-3, simian immunodeficiency virus (SIV) or feline immunodeficiency virus (FIV), and where the lentivirus is HIV, the medicament is for preventing the onset of acquired immunodeficiency syndrome (AIDS). The infectious disease is also a non-viral pathogen such as protozoal, bacterial or fungal infection, and is caused by a species of Leishmania, leprosy, Cryptosporidium, Coccidioides immitis, listeria, coccidomycosis or mycobacterium, preferably tuberculosis. The medicament is also for treating an autoimmune disease, preferably lupus, or for treating an allergic disease such as allergic rhinitis or atopic dermatitis, or for treating cancer patients immunocompromised because of chemotherapy. The medicament is also for treating cardiac patients, where the cardiac patient has been infected by a virus which causes inflammatory heart disease. The medicament is preferably a vaccine, where the dimers serve as an adjuvant, and the vaccine is a flu vaccine. The auto-antibodies against the family of TCR V beta CDR peptides are generated as a result of contact between the animal and an oil or adjuvant. The medicament is additionally for treating immune dysfunction and abnormal cytokine production induced by the aging process. The T-cell receptor V beta CDR1 peptide or its variant is useful in the treatment or prevention of a viral or non-viral pathogenic disease such as a protozoal infection (Leishmaniasis), a bacterial or fungal infection (coccidiomycosis), leprosy, an autoimmune disease (rheumatoid arthritis, Crohn's disease, insulin-dependent diabetes mellitus, multiple sclerosis, atherosclerosis, Hashimoto's thyroiditis, celiac disease, myasthenia gravis, pemphigus vulgaris, systemic lupus erythematosus (SLE), Grave's disease, systemic vasculitis, reduction of immunocompetence due to contact to environmental agents for example oils and adjuvants, an allergic disease (asthma, allergic rhinitis or atopic dermatitis), cancer (lymphoid tumor, melanoma or breast cancer), cardiac conditions, or as an adjuvant, for example in flu or other vaccine (all claimed).
Dwg.0/7

L2 ANSWER 2 OF 5 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 2002-139689 [18] WPIDS
DNN N2002-105310 DNC C2002-042994
TI New T-cell receptor-derived peptides for preventing and/or treating human immunodeficiency virus infection, cardiovascular diseases and disorders and allergic disease.
DC B04 P31
IN **MARCHALONIS, J J**; SCHLUTER, S F; WATSON, R R
PA (ARIZ-N) ARIZONA BOARD OF REGENTS
CYC 95
PI WO 2001095785 A2 20011220 (200218)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001066845 A 20011224 (200227)

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

ADT WO 2001095785 A2 WO 2001-US18817 20010612; AU 2001066845 A AU 2001-66845 20010612; EP 1357929 A2 EP 2001-944433 20010612, WO 2001-US18817 20010612

FDT AU 2001066845 A Based on WO 2001095785; EP 1357929 A2 Based on WO 2001095785

PRAI US 2000-591789 20000612

AB WO 200195785 A UPAB: 20020319

NOVELTY - A purified T-cell receptor (TCR)-derived peptide (I) or its derivative, is new.

DETAILED DESCRIPTION - (I) comprises the amino acid sequence chosen from:

(1) Cys-Lys-Pro-Ile-Ser-Gly-His-Asn-Ser-Leu-Phe-Trp-Tyr-Arg-Gln-Thr;
(2) Ala-Asn-Tyr-Gly-Tyr-Thr-Phe-Gly-Ser-Gly-Thr-Arg-Leu-Thr-Val-Val;
(3) Leu-Lys-Ile-Gln-Pro-Ser-Glu-Pro-Arg-Asp-Ser-Ala-Val-Tyr-Leu-Cys-Ala;
(4) Leu-Thr-Ile-Gln-Arg-Thr-Gln-Gln-Glu-Asp-Ser-Ala-Val-Tyr-Leu-Cys-Ala;
(5) Leu-Ile-Leu-Glu-Ser-Ala-Ser-Thr-Asn-Gln-Thr-Ser-Met-Tyr-Leu-Cys-Ala;
(6) Leu-Thr-Val-Ser-Gly-Leu-Gln-Ala-Glu-Asp-Glu-Ala-Asp-Tyr-Tyr-Cys-Ser;
(7) Leu-Ala-Ile-Ser-Gly-Leu-Glu-Ser-Glu-Asp-Glu-Ala-Asp-Tyr-Tyr-Cys-Ser;
(8) Phe-Thr-Ile-Ser-Gly-Leu-Gln-Pro-Glu-Asp-Ile-Ala-Thr-Tyr-Tyr-Cys-Gln;
(9) Leu-Thr-Ile-Ser-Gly-Leu-Glu-Pro-Glu-Asp-Phe-Ala-Val-Tyr-Tyr-Cys-Gln;
(10) Leu-Lys-Ile-Ser-Arg-Val-Glu-Ala-Glu-Asp-Le-Gly-Val-Tyr-Phe-Cys-Ser;
(11) Leu-Thr-Ile-Asn-Pro-Val-Glu-Ala-Asp-As-Val-Ala-Thr-Tyr-Tyr-Cys-Gln;
(12) Ala-Asn-Tyr-Gly-Tyr-Thr-Phe-Gly-Ser-Gly-Thr-Lys-Leu-Thr-Val-Val;
(13) Ala-Asn-Tyr-Gly-Tyr-Thr-Phe-Gly-Ser-Gly-Thr-Glu-Leu-Thr-Val-Val;
(14) Ala-Asn-Tyr-Gly-Tyr-Thr-Phe-Gly-Ser-Gly-Thr-Asp-Leu-Thr-Val-Val;

and

(15) Thr-Phe-Gly-Xaa-Gly-Thr-Yaa.

Where:

Xaa = any amino acid; and
Yaa = Arg, Lys, Asp, Glu, His or other charged amino acid molecule.

ACTIVITY - Anti-HIV; Antiatherosclerotic; Cardiant; Antiarteriosclerotic; Vasotropic; Antiallergic; Antiasthmatic; Immunosuppressive; Cytostatic; Antianaphylactic; Antibacterial; Virucide; Fungicide. No supporting data is given.

MECHANISM OF ACTION - Promoter of Th1 cytokine production; Inhibitor of Th2 cytokine and IgE production; Inhibitor of solid tumor growth.

USE - (I) is useful for increasing production of Th1 cytokines such as interleukin-2 (IL-2) and interferon- gamma , or to decrease production of Th2 cytokines such as IL-4, IL-5, IL-6, IL-10 or immunoglobulin G, in an individual free of infection with an immunodeficiency-type retrovirus and delaying the onset of acquired immunodeficiency syndrome (AIDS) in humans by administering the peptide to a human infected with immunodeficiency-type retrovirus, preferably HIV or feline immunodeficiency virus, to delay the onset of AIDS. (I) is also useful for reversing the deleterious effects of infection with an immunodeficiency-type retrovirus (HIV), preventing or treating a disease or disorder of the cardiovascular system, such as atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, thrombus formation and retrovirus-induced cardiovascular dysfunction, and allergic disease or disorder characterized by increased immunoglobulin E (IgE) production such as allergy, asthma, delayed hypersensitivity, septic shock and anaphylactic shock. (I) is further useful for inhibiting the growth of a solid tumor or reducing the volume of a solid tumor such as sarcomas, carcinomas, lymphomas, and other solid tumor cancers, tumors of the germ

ovarian, testicular, thyroid, pancreatic, stomach, liver or colon cancer tumor, astrocytoma, glioma or melanoma tumor, and also for preventing immunosuppression or suppressing progression to immune dysfunction or cytokine dysregulation in an individual infected with a viral, fungal or bacterial infectious agent other than an immunodeficiency-type retrovirus (claimed).
Dwg.0/0

L2 ANSWER 3 OF 5 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1999-357172 [30] WPIDS
DNC C1999-105556
TI Delaying onset of AIDS in a host infected with an immunodeficiency-type retrovirus.
DC B04
IN DEHGHANPISHEH, K; HUANG, D S; **MARCHALONIS, J J**; WANG, Y; WATSON, R R
PA (ARIZ-N) ARIZONA BOARD OF REGENTS
CYC 1
PI US 5911990 A 19990615 (199930)* 13p
ADT US 5911990 A US 1996-696049 19960813
PRAI US 1996-696049 19960813
AB US 5911990 A UPAB: 19990802
NOVELTY - Administration of a peptide (I) corresponding to the first complementarity determining region of T-cell receptor V beta (TCR V beta CDR1) to a host infected with an immunodeficiency type retrovirus results in the prevention of retrovirus-induced suppression of immune responses and normalizes cytokine production.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) a method of modulating the immune response of a mammal infected with a C-type retrovirus or a lentivirus by administering (I) through a systemic route to stimulate production of T helper 1 (Th1) cytokines; interleukin 2 and interferon- gamma , and to suppress the production of T helper 2 (Th2); interleukins 5, 6 and 10 and immunoglobulin G; and

(2) a method of altering the immune system response of a host suffering from an infectious disease by artificially introducing (I) by injection into the host's bloodstream or immune system so that the immune system is artificially induced to stimulate production of Th1 cytokines or suppress production of Th2 derived cytokines.

ACTIVITY - Anti-HIV.

MECHANISM OF ACTION - Immunomodulating agent.

(I) reduces the imbalance of Th1 and Th2 cytokine production and contributes to the normalization of the immune response which retards development of immune dysfunction.

Female C57B1/6 5 week old mice were set up in 3 treatments: (1) LP-BM5 retrovirus infected mice injected with saline, (2) LP-BM5 retrovirus infected mice injected with control peptide MCG3, or (3) LP-BM5 retrovirus infected mice injected with TCR V beta CDR1. Administration of peptides (200 micro g/mice in saline, i.p.) was carried out twice on days 7 and 3 before retrovirus infection. Peptide preparations were free of endotoxins and for TCR V beta CDR1 comprised the sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr corresponding to the human TCR V beta sequence and for the control sequence Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr corresponding to the CDR1 of the L chain MCG. The LP-BM5 retrovirus was administered i.p. to mice on 0.1 ml with an electrophic titer of 4.5 log10 PFU/ml which leads to rapid induction of clinical symptoms with virtually no latent phase.

After 42 days of retroviral infection immunological analysis was carried out. Specific titers of serum IgG to TCR- beta and MCG3 were determined by enzyme linked immunosorbent assay (ELISA). IgG production by LPS-stimulated splenocytes, an indication of early retrovirus infection during the progression to murine AIDS, was significantly reduced (p less than 0.05) by TCR V beta administration before infection but administration of control peptide MCG3 showed no effect.

Treatment of retrovirally infected mice with (I) did not result in a significant increase in mean Ab titers compared with either retrovirally

mice. In vitro production of Th1 cytokines, Il-2 and IFN- gamma by concanavalin A-stimulated splenocytes was significantly (p less than 0.05) inhibited and normalized in the retrovirus infected mice administered with TCR V beta before infection but not in those administered the control peptide MCG3. Release of TNF- alpha by LPS-stimulated splenocytes was significantly inhibited in retrovirally infected mice administered with TCR V beta (p less than 0.05).

USE - Administration of (I) is used to delay the onset of AIDS through the restoration of normal levels of Th1 cytokines and Th2 derived cytokines and extends the period that occurs between infection by the retrovirus and the appearance of immune deficiencies. It causes the deleterious effects of infection to be reversed through prevention of immunosuppression and cytokine dysregulation that is otherwise induced by infection with an immunodeficiency-type retrovirus.

Studying (I) gives an insight into the pathogenesis occurring that leads to AIDS and into the idiotypic networks that involve autoantibodies and autoreactive T cells as regulatory elements and an understanding of the role of Vitamin E in immune function during retrovirus infection.
Dwg.0/0

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=> d his

     (FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

     FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
                E MARCHALONIS JOHN J/IN
L1             2 S E3

     FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
                E MARCHALONIS J J/IN
L2             5 S E2 OR E3

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    29.07      45.17

FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004

 FILE LAST UPDATED: 4 MAR 2004 (20040304/UP).  FILE COVERS 1953 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> e marchalonis j j/au
E1             1     MARCHALL GUY/AU
E2             8     MARCHALONIS J/AU
E3           238 --> MARCHALONIS J J/AU
E4             9     MARCHALONIS JOHN J/AU
E5             1     MARCHALONIS JOHN JACOB/AU
E6             1     MARCHALOT GENEVIEVE/AU
E7             4     MARCHALUK E/AU
E8             1     MARCHALUK WISNIEWSKA E/AU
E9             1     MARCHAM P/AU
E10            1     MARCHAN A/AU
E11            2     MARCHAN C/AU
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=> s e2-e5
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           238 "MARCHALONIS J J"/AU
             9 "MARCHALONIS JOHN J"/AU
             1 "MARCHALONIS JOHN JACOB"/AU
L3   256 ("MARCHALONIS J"/AU OR "MARCHALONIS J J"/AU OR "MARCHALONIS
               JOHN J"/AU OR "MARCHALONIS JOHN JACOB"/AU)

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         16179 TCR
       3600566 T
       1750104 CELL
        449346 RECEPTOR
         15796 T-CELL RECEPTOR
                 (T(W)CELL(W)RECEPTOR)
L4   75 L3 AND (TCR OR T-CELL RECEPTOR)

=> s l4 and (TH1 or TH2 or T helper or TH1/TH2)
'TH2' IS NOT A VALID FIELD CODE
         12397 TH1
         11454 TH2
       3600566 T
         26901 HELPER
         10146 T HELPER
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             0 TH1/TH2
L5   4 L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)

=> s l4 and (TH1 (w) TH2)
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         11454 TH2
          1527 TH1 (W) TH2
L6   0 L4 AND (TH1 (W) TH2)

=> d l5,ti,1-4

L5   ANSWER 1 OF 4   MEDLINE on STN
TI   **T-cell receptor** V beta 8.1 peptide reduces coxsackievirus-induced
     cardiopathology during murine acquired immunodeficiency syndrome.

L5   ANSWER 2 OF 4   MEDLINE on STN
TI   Effects of vaccination against different T cell receptors on maintenance
     of immune function during murine retrovirus infection.

L5   ANSWER 3 OF 4   MEDLINE on STN
TI   **T-cell-receptor** dose and the time of treatment during murine
     retrovirus infection for maintenance of immune function.

L5   ANSWER 4 OF 4   MEDLINE on STN
TI   **T cell receptor** V beta complementarity-determining region 1 peptide
     administration moderates immune dysfunction and cytokine dysregulation
     induced by murine retrovirus infection.

=> d l5,cbib,ab,1-4

L5   ANSWER 1 OF 4   MEDLINE on STN
2003092748.   PubMed ID: 12605029.   **T-cell receptor** V beta 8.1 peptide
     reduces coxsackievirus-induced cardiopathology during murine acquired
     immunodeficiency syndrome. Sepulveda Ramon Tomas; **Marchalonis John
     Jacob**; Watson Ronald Ross. (College of Public Health, College of
     Medicine, University of Arizona, Tucson, Arizona 85724, USA.) Journal of
     cardiovascular pharmacology, (2003 Mar) 41 (3) 489-97. Journal code:
     7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB [illegible] LP-BM5 infection in mice results in progressive deterioration of the immune system in the majority of untreated hosts. Peptide immunotherapy has been shown to be effective in the stimulation or immunoregulation of **T-helper** 1 (T(H)1) and **T-helper** 2 (T(H) 2) response subsets. In murine acquired immunodeficiency syndrome (AIDS), T(H)1 deficiency enables the host to be susceptible to coxsackievirus infection, inducing cardiopathology in a short period. **T-cell receptor** (**TCR**) Vbeta8.1 peptide, a 16-mer peptide containing the entire CDR1 segment and part of the FR2 region of human Vbeta8, showed both an immunoregulating and immunostimulating effect in murine AIDS. **TCR** Vbeta8.1 peptide acts on T cells promoting interleukin-2 production and therefore enhancing a cell-mediated immune response. It retarded development of cardiopathology due to coxsackievirus infection. Retrovirus-infected mice treated with the peptide showed a longer life span than the nontreated, retrovirus-infected animals.

L5 ANSWER 2 OF 4 MEDLINE on STN

96400439. PubMed ID: 8806815. Effects of vaccination against different T cell receptors on maintenance of immune function during murine retrovirus infection. Liang B; **Marchalonis J J**; Zhang Z; Watson R R. (Department of Family and Community Medicine, University of Arizona, Tucson 85724, USA.) Cellular immunology, (1996 Aug 25) 172 (1) 126-34. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Murine retrovirus infection causes an aberrant stimulation of several subsets of **T helper** 2 cells identified by their T cell receptors (**TCR**). C57BL/6 mice were treated with synthetic peptides based upon different human **TCR** V beta CDR1 sequences following experimental infection with the murine retrovirus. Previous studies established that retrovirally infected mice produced autoantibodies to certain of these peptides, and their administration after infection diminished many of the cytokine abnormalities induced by the virus. This study determined whether the complete 16-mer synthetic peptides modeling the V beta CDR1/FR3 were required, and whether admixture of autoantigenic peptides synergized immune preservation. Treatment with complete **TCR** pep beta 3 and pep V beta 5.2 peptide alone and combined largely prevented the retrovirus-induced reduction in B and T cell proliferation and **Th1** cytokine secretion while suppressing excessive production of **Th2** cytokines, which are stimulated by retrovirus infection. Treatment with overlapping short peptides corresponding to the N-terminal 11-mer and C-terminal 12-mer did not significantly prevent the immune dysfunction in retrovirus-infected mice. These data suggest that immune dysfunction and abnormal cytokine production, induced by murine retrovirus infection, were largely prevented by **TCR** V beta CDR1 peptides, and the complete CDR1 in association with the five residues from FR2 was required.

L5 ANSWER 3 OF 4 MEDLINE on STN

96245971. PubMed ID: 8698380. **T-cell-receptor** dose and the time of treatment during murine retrovirus infection for maintenance of immune function. Liang B; Ardestani S; **Marchalonis J J**; Watson R R. (Department of Family and Community Medicine, University of Arizona, Tucson 85724, USA.) Immunology, (1996 Feb) 87 (2) 198-204. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB C57BL/6 mice were injected with different doses of human **T-cell receptor** (**TCR**) V beta 8.1 CDR1 peptide at different times after murine retrovirus (LP-BM5) infection. Injection with **TCR** V beta 8.1 CDR1 peptide largely prevented the retrovirus-induced reduction in B- and T-cell proliferation, and **T-helper** 1 (**Th1**) cytokines [interleukin-2 (IL-2) and interferon-gamma (IFN-gamma)] secretion. It also suppressed **T-helper** 2 (**Th2**) cytokines (IL-6 and IL-10) production, which was stimulated by retrovirus infection. These effects were accomplished using at least 100 micrograms of peptide per mouse and the most effective dose of peptide had to be given within 4 weeks after retrovirus infection. Immunization with doses above 100 micrograms/mouse as long as 4 weeks postinfection maintained natural killer (NK) cell activity during retrovirus infection. Reducing the dose of peptide or delaying it until

the disease progressed towards fatal murine acquired immune deficiency syndrome (AIDS) allowed development of immune dysfunction. These studies provide data suggesting that immune dysfunction, induced by murine retrovirus infection, was largely prevented by **TCR** V beta CDR1 peptide injection.

L5 ANSWER 4 OF 4 MEDLINE on STN
95363196. PubMed ID: 7636274. **T cell receptor** V beta complementarity-determining region 1 peptide administration moderates immune dysfunction and cytokine dysregulation induced by murine retrovirus infection. Watson R R; Wang J Y; Dehghanpisheh K; Huang D S; Wood S; Ardestani S K; Liang B; **Marchalonis J J**. (Department of Family and Community Medicine, University of Arizona College of Medicine, Tucson 85724, USA.) Journal of immunology (Baltimore, Md. : 1950), (1995 Aug 15) 155 (4) 2282-91. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Murine AIDS, induced by LP-BM5 murine leukemia retrovirus infection, causes a progressive and profound immunodeficiency in female C57B1/6 mice. Previously, we reported that autoantibodies were elevated during the initiation phases of this murine retrovirus infection and bound peptide determinants corresponding to CDR1 of several **TCR** V beta-chains. Therefore, we designed studies to determine whether administration of a major autoimmunogenic **TCR** V beta CDR1 peptide before or after infection with LP-BM5 retrovirus would modulate retrovirus-induced dysregulation of T cell function. Administration of the **TCR** V beta CDR1 peptide before murine retrovirus infection significantly prevented its suppression of splenic NK cell activity, T and B cell proliferation, and monokine (IL-6 and TNF-alpha) and **Th1** cytokine (IL-2 and IFN-gamma) release by splenocytes, and inhibited retrovirus-induced elevation of **Th2** cytokine (IL-5 and IL-10). Similar data were obtained with peptide immunization 2 wk after murine retrovirus infection at 6 and 16 wk postinfection. However, delaying peptide immunization until severe suppression of T and B cell mitogenesis had occurred did not restore their functions. Immunization with **TCR** V beta peptide prevents development of retrovirus-induced immune dysfunction, which suggests a possible pathogenic role of autoreactive T cells as regulatory elements.

=> d his

(FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
E MARCHALONIS JOHN J/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
E MARCHALONIS J J/IN
L2 5 S E2 OR E3

FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
E MARCHALONIS J J/AU
L3 256 S E2-E5
L4 75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5 4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6 0 S L4 AND (TH1 (W) TH2)

=> file uspatful

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.96	52.13

FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Mar 2004 (20040304/PD)

FILE LAST UPDATED: 4 MAR 2004 (20040304/ED)
HIGHEST GRANTED PATENT NUMBER: US6701528
HIGHEST APPLICATION PUBLICATION NUMBER: US2004045070
CA INDEXING IS CURRENT THROUGH 4 Mar 2004 (20040304/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Mar 2004 (20040304/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s (TCR or T-cell receptor)
          4879 TCR
        922700 T
        456541 CELL
         90018 RECEPTOR
          7030 T-CELL RECEPTOR
                 (T(W)CELL(W)RECEPTOR)
L7        9668 (TCR OR T-CELL RECEPTOR)

=> s l7 and (peptide? or polypeptide?)
         99650 PEPTIDE?
         68173 POLYPEPTIDE?
L8        7692 L7 AND (PEPTIDE? OR POLYPEPTIDE?)

=> s l8 and (V beta)
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        316807 BETA
          2799 V BETA
                 (V(W)BETA)
L9         816 L8 AND (V BETA)

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       1814907 DETERMIN?
        795458 REGION
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L10        123 L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)

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          5434 TH2
        922700 T
         18147 HELPER
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         922700 T
          18147 HELPER
        3718780 2
            217 T HELPER 2
                  (T(W)HELPER(W)2)
L11          39 L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)

=> d l11,ti,1-30

L11  ANSWER 1 OF 39  USPATFULL on STN
TI     Methods of diagnosis of breast cancer, compositions and methods of
       screening for modulators of breast cancer

L11  ANSWER 2 OF 39  USPATFULL on STN
TI     Compositions and methods for WT1 specific immunotherapy

L11  ANSWER 3 OF 39  USPATFULL on STN
TI     Compositions and methods for the detection, diagnosis and therapy of
       hematological malignancies

L11  ANSWER 4 OF 39  USPATFULL on STN
TI     Atherosclerosis vaccine

L11  ANSWER 5 OF 39  USPATFULL on STN
TI     Compositions and methods for the detection, diagnosis and therapy of
       hematological malignancies

L11  ANSWER 6 OF 39  USPATFULL on STN
TI     Compositions and methods for WT1 specific immunotherapy

L11  ANSWER 7 OF 39  USPATFULL on STN
TI     Novel nucleic acids and polypeptides

L11  ANSWER 8 OF 39  USPATFULL on STN
TI     Compositions and methods for WT1 specific immunotherapy

L11  ANSWER 9 OF 39  USPATFULL on STN
TI     Compositions and methods for WT1 specific immunotherapy

L11  ANSWER 10 OF 39  USPATFULL on STN
TI     Methods of selecting T cell receptor V peptides for therapeutic use

L11  ANSWER 11 OF 39  USPATFULL on STN
TI     Method of treating immune pathologies with low dose estrogren

L11  ANSWER 12 OF 39  USPATFULL on STN
TI     Compositions and methods for treatment of neoplastic disease

L11  ANSWER 13 OF 39  USPATFULL on STN
TI     Autologous adoptive immunotherapy with antigen-specific primed T cells
       or B cells to promote antigen-specific immune responses with an
       appropriate cytokine bias

L11  ANSWER 14 OF 39  USPATFULL on STN
TI     T cell receptor Vbeta-Dbeta-Jbeta sequence and methods for its detection

L11  ANSWER 15 OF 39  USPATFULL on STN
TI     Compositions and methods for diagnosis and therapy of malignant
       mesothelioma

L11  ANSWER 16 OF 39  USPATFULL on STN
TI     Compositions and methods for the detection, diagnosis and therapy of
       hematological malignancies
```

L11 ANSWER 17 OF 39 USPATFULL on STN
TI Methods of administering/dosing CD2 antagonists for the prevention and treatment of autoimmune disorders or inflammatory disorders

L11 ANSWER 18 OF 39 USPATFULL on STN
TI Anergy-regulated molecules

L11 ANSWER 19 OF 39 USPATFULL on STN
TI **T cell receptor** Vβ-Dβ-Jβ sequence and methods for its detection

L11 ANSWER 20 OF 39 USPATFULL on STN
TI Novel complex-forming proteins

L11 ANSWER 21 OF 39 USPATFULL on STN
TI Methods of preventing or treating inflammatory or autoimmune disorders by administering CD2 antagonists in combination with other prophylactic or therapeutic agents

L11 ANSWER 22 OF 39 USPATFULL on STN
TI Compositions and methods for WT1 specific immunotherapy

L11 ANSWER 23 OF 39 USPATFULL on STN
TI Recombinant MHC molecules useful for manipulation of antigen-specific T-cells

L11 ANSWER 24 OF 39 USPATFULL on STN
TI Compositions and methods for the detection, diagnosis and therapy of hematological malignancies

L11 ANSWER 25 OF 39 USPATFULL on STN
TI Compositions and methods for the therapy and diagnosis of Her-2/neu-associated malignancies

L11 ANSWER 26 OF 39 USPATFULL on STN
TI Complex-forming proteins

L11 ANSWER 27 OF 39 USPATFULL on STN
TI Compositions and methods for treatment of neoplastic disease

L11 ANSWER 28 OF 39 USPATFULL on STN
TI Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein

L11 ANSWER 29 OF 39 USPATFULL on STN
TI Recombinant MHC molecules useful for manipulation of antigen-specific T-cells

L11 ANSWER 30 OF 39 USPATFULL on STN
TI Methods of preventing or treating inflammatory or autoimmune disorders by administering integrin alphanubeta3 antagonists in combination with other prophylactic or therapeutic agents

=> d l11,ti,1-39

L11 ANSWER 1 OF 39 USPATFULL on STN
TI Methods of diagnosis of breast cancer, compositions and methods of screening for modulators of breast cancer

L11 ANSWER 2 OF 39 USPATFULL on STN
TI Compositions and methods for WT1 specific immunotherapy

L11 ANSWER 3 OF 39 USPATFULL on STN
TI Compositions and methods for the detection, diagnosis and therapy of

hematological malignancies

L11 ANSWER 4 OF 39 USPATFULL on STN
TI Atherosclerosis vaccine

L11 ANSWER 5 OF 39 USPATFULL on STN
TI Compositions and methods for the detection, diagnosis and therapy of hematological malignancies

L11 ANSWER 6 OF 39 USPATFULL on STN
TI Compositions and methods for WT1 specific immunotherapy

L11 ANSWER 7 OF 39 USPATFULL on STN
TI Novel nucleic acids and **polypeptides**

L11 ANSWER 8 OF 39 USPATFULL on STN
TI Compositions and methods for WT1 specific immunotherapy

L11 ANSWER 9 OF 39 USPATFULL on STN
TI Compositions and methods for WT1 specific immunotherapy

L11 ANSWER 10 OF 39 USPATFULL on STN
TI Methods of selecting **T cell receptor** V **peptides** for therapeutic use

L11 ANSWER 11 OF 39 USPATFULL on STN
TI Method of treating immune pathologies with low dose estrogren

L11 ANSWER 12 OF 39 USPATFULL on STN
TI Compositions and methods for treatment of neoplastic disease

L11 ANSWER 13 OF 39 USPATFULL on STN
TI Autologous adoptive immunotherapy with antigen-specific primed T cells or B cells to promote antigen-specific immune responses with an appropriate cytokine bias

L11 ANSWER 14 OF 39 USPATFULL on STN
TI **T cell receptor** Vbeta-Dbeta-Jbeta sequence and methods for its detection

L11 ANSWER 15 OF 39 USPATFULL on STN
TI Compositions and methods for diagnosis and therapy of malignant mesothelioma

L11 ANSWER 16 OF 39 USPATFULL on STN
TI Compositions and methods for the detection, diagnosis and therapy of hematological malignancies

L11 ANSWER 17 OF 39 USPATFULL on STN
TI Methods of administering/dosing CD2 antagonists for the prevention and treatment of autoimmune disorders or inflammatory disorders

L11 ANSWER 18 OF 39 USPATFULL on STN
TI Anergy-regulated molecules

L11 ANSWER 19 OF 39 USPATFULL on STN
TI **T cell receptor** Vβ-Dβ-Jβ sequence and methods for its detection

L11 ANSWER 20 OF 39 USPATFULL on STN
TI Novel complex-forming proteins

L11 ANSWER 21 OF 39 USPATFULL on STN
TI Methods of preventing or treating inflammatory or autoimmune disorders by administering CD2 antagonists in combination with other prophylactic or therapeutic agents

L11 ANSWER 22 OF 39 USPATFULL on STN

TI Compositions and methods for wt1 specific immunotherapy

L11 ANSWER 23 OF 39 USPATFULL on STN
TI Recombinant MHC molecules useful for manipulation of antigen-specific T-cells

L11 ANSWER 24 OF 39 USPATFULL on STN
TI Compositions and methods for the detection, diagnosis and therapy of hematological malignancies

L11 ANSWER 25 OF 39 USPATFULL on STN
TI Compositions and methods for the therapy and diagnosis of Her-2/neu-associated malignancies

L11 ANSWER 26 OF 39 USPATFULL on STN
TI Complex-forming proteins

L11 ANSWER 27 OF 39 USPATFULL on STN
TI Compositions and methods for treatment of neoplastic disease

L11 ANSWER 28 OF 39 USPATFULL on STN
TI Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein

L11 ANSWER 29 OF 39 USPATFULL on STN
TI Recombinant MHC molecules useful for manipulation of antigen-specific T-cells

L11 ANSWER 30 OF 39 USPATFULL on STN
TI Methods of preventing or treating inflammatory or autoimmune disorders by administering integrin alphanubeta3 antagonists in combination with other prophylactic or therapeutic agents

L11 ANSWER 31 OF 39 USPATFULL on STN
TI Compositions and methods of monoclonal and polyclonal antibodies specific for T cell subpopulations

L11 ANSWER 32 OF 39 USPATFULL on STN
TI Methods for treating inflammation

L11 ANSWER 33 OF 39 USPATFULL on STN
TI Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein

L11 ANSWER 34 OF 39 USPATFULL on STN
TI **T-cell receptor** Vβ-Dβ-Jβ sequence and methods for its detection

L11 ANSWER 35 OF 39 USPATFULL on STN
TI Recombinant MHC molecules useful for manipulation of antigen-specific T-cells

L11 ANSWER 36 OF 39 USPATFULL on STN
TI Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein

L11 ANSWER 37 OF 39 USPATFULL on STN
TI Methods for treatment of multiple sclerosis utilizing **peptide** analogues of human myelin basic protein

L11 ANSWER 38 OF 39 USPATFULL on STN
TI DNA vaccination for induction of suppressive T cell response

L11 ANSWER 39 OF 39 USPATFULL on STN
TI **T-cell receptor peptides** and methods for preventing the progression to AIDS in an animal model

```
=> d his

     (FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

     FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
                E MARCHALONIS JOHN J/IN
L1             2 S E3

     FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
                E MARCHALONIS J J/IN
L2             5 S E2 OR E3

     FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
                E MARCHALONIS J J/AU
L3           256 S E2-E5
L4            75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5             4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6             0 S L4 AND (TH1 (W) TH2)

     FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7          9668 S (TCR OR T-CELL RECEPTOR)
L8          7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9           816 S L8 AND (V BETA)
L10          123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11           39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)

=> s l11 not l1
L12           38 L11 NOT L1

=> d l12,cbib,ab,clm,1-38

L12  ANSWER 1 OF 38  USPATFULL on STN
2004:38576 Methods of diagnosis of breast cancer, compositions and methods of
    screening for modulators of breast cancer.
    Mack, David H., Menlo Park, CA, UNITED STATES
    Gish, Kurt C., San Francisco, CA, UNITED STATES
    Afar, Daniel, Brisbane, CA, UNITED STATES
    Eos Technology, Inc., South San Francisco, CA, UNITED STATES, 94080-7019
    (U.S. corporation)
    US 2004029114 A1 20040212
    APPLICATION: US 2002-58270  A1  20020124 (10)
    PRIORITY: US 2001-263965P  20010124 (60)
    US 2001-265928P  20010202 (60)
    US 2001-282698P  20010409 (60)
    US 2001-288590P  20010504 (60)
    US 2001-294443P  20010529 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Described herein are genes whose expression are up-regulated or
       down-regulated in breast cancer. Related methods and compositions that
       can be used for diagnosis and treatment of breast cancer are disclosed.
       Also described herein are methods that can be used to identify
       modulators of breast cancer.
CLM    What is claimed is:
       1. A method of detecting a breast cancer-associated transcript in a cell
       from a patient, the method comprising contacting a biological sample
       from the patient with a polynucleotide that selectively hybridizes to a
       sequence at least 80% identical to a sequence as shown in Tables 1-25.

       2. The method of claim 1, wherein the biological sample comprises
       isolated nucleic acids.

       3. The method of claim 2, wherein the nucleic acids are mRNA.
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4. The method of claim 2, further comprising the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

5. The method of claim 1, wherein the polynucleotide comprises a sequence as shown in Tables 1-25.

6. The method of claim 1, wherein the polynucleotide is immobilized on a solid surface.

7. The method of claim 1, wherein the patient is undergoing a therapeutic regimen to treat breast cancer.

8. The method of claim 1, wherein the patient is suspected of having breast cancer.

9. An isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Tables 1-25.

10. The nucleic acid molecule of claim 9, which is labeled.

11. An expression vector comprising the nucleic acid of claim 9.

12. A host cell comprising the expression vector of claim 11.

13. An isolated **polypeptide** which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1-25.

14. An antibody that specifically binds a **polypeptide** of claim 13.

15. The antibody of claim 14, further conjugated to an effector component.

16. The antibody of claim 15, wherein the effector component is a fluorescent label.

17. The antibody of claim 15, wherein the effector component is a radioisotope or a cytotoxic chemical.

18. The antibody of claim 15, which is an antibody fragment.

19. The antibody of claim 15, which is a humanized antibody

20. A method of detecting a breast cancer cell in a biological sample fromi a patient, the method comprising contacting the biological sample with an antibody of claim 14.

21. The method of claim 20, wherein the antibody is further conjugated to an effector component.

22. The method of claim 21, wherein the effector component is a fluorescent label.

23. A method for identifying a compound that modulates a breast cancer-associated **polypeptide**, the method comprising the steps of: (i) contacting the compound with a breast cancer-associated **polypeptide**, the **polypeptide** encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-25; and (ii) determining the functional effect of the compound upon the **polypeptide**.

24. A drug screening assay comprising the steps of (i) administering a test compound to a mammal having breast cancer or a cell isolated therefrom; (ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-25 in a treated cell or

mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that modulates the level of expression of the polynucleotide is a candidate for the treatment of breast cancer.

L12 ANSWER 2 OF 38 USPATFULL on STN
2004:24366 Compositions and methods for WT1 specific immunotherapy.
Gaiger, Alexander, Vienna, AUSTRIA
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Jaya, Nomalie, Seattle, WA, UNITED STATES
Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)
US 2004018204 A1 20040129
APPLICATION: US 2003-427717 A1 20030430 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compositions comprise one or more of a WT1 polynucleotide, a WT1 **polypeptide**, an antigen-presenting cell presenting a WT1 **polypeptide**, an antibody that specifically binds to a WT1 **polypeptide**; or a T cell that specifically reacts with a WT1 **polypeptide**. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.

CLM What is claimed is:

1. An isolated **polypeptide** comprising an immunogenic portion of a Wilms' tumor antigen, selected from the group consisting of SEQ ID NOs:478 and 502, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with WT1-specific antisera and/or T-cell lines or clones is not substantially diminished.

2. The isolated **polypeptide** according to claim 1 wherein the immunogenic portion has been modified such that the ability of the immunogenic portion to bind to an MHC molecule is increased relative to that of the immunogenic portion.

3. The isolated **polypeptide** according to claim 2 wherein the immunogenic portion has been modified such that the ability of the immunogenic portion to bind to HLA-A2 is increased relative to that of the unmodified immunogenic portion.

4. An isolated **polypeptide** comprising a Wilms' tumor antigen having a deletion of a proline rich region.

5. An isolated **polypeptide** according to claim 4 wherein said proline rich region is from about amino acid positions 54 to 68 of the Wilms' tumor antigen.

6. The isolated **polypeptide** of claim 5 wherein said **polypeptide** comprises the amino acid sequence set forth in any one of SEQ ID NO:478 and 502.

7. A fusion protein comprising at least one **polypeptide** according to any one of claims 1, 2 or 4.

8. The fusion protein of claim 7 wherein said fusion partner is selected from the group consisting of Ra12, protein D, LYTA, a HIS tag, a targeting signal capable of directing a **polypeptide** to the endosomal/lysosomal compartment, twin arginine translocator, and truncated twin arginine translocator.

9. The fusion protein of claim 8 wherein the fusion protein comprises a twin arginine translocator signal **peptide**.

10. The fusion protein of claim 8 wherein the fusion partner comprises the amino acid sequence of any one of SEQ ID NOs:504 and 506.

11. The fusion protein of claim 10 wherein the fusion protein comprises the amino acid sequence of any one of SEQ ID NOs:470, 479-483, and 499.

12. An isolated polynucleotide encoding the fusion proteins of any one of claims 7, 9, and 11.

13. The isolated polynucleotide of claim 12 wherein the polynucleotide has been codon optimized for expression in E. coli.

14. The isolated polynucleotide of claim 12 wherein the polynucleotide comprises a sequence of any one of SEQ ID NOs: 469, 471, and 472-477 and 503, 505.

15. A composition comprising a **polypeptide** of claim 1, 4, 6, or 11 in combination with a pharmaceutically acceptable carrier or excipient.

16. A vaccine comprising a **polypeptide** of claim 1, 4, 6, or 11 in combination with a non-specific immune response enhancer.

17. The vaccine according to claim 15 wherein the non-specific immune response enhancer preferentially enhances a T cell response in a patient.

18. The vaccine according to claim 15, wherein the immune response enhancer is selected from the group consisting of 3d-MPL, MPL, RC-529, AGP's, Montamide ISA50, Seppic Montamide ISA 720, a cytokine, a microsphere, dimethyl dioctadecyl ammoniumbromide (DDA) based adjuvants, AS-1, AS-2, Ribi Adjuvant system based adjuvant, QS21, saponin based adjuvants, Syntex adjuvant in its microfluidized form, MV, ddMV, immune stimulating complex (iscom) based adjuvants, and inactivated toxins.

19. An expression vector comprising a polynucleotide of claim 12 operably linked to an expression control sequence.

20. A host cell transformed or transfected with an expression vector according to claim 19.

L12 ANSWER 3 OF 38 USPATFULL on STN
2004:7328 Compositions and methods for the detection, diagnosis and therapy of hematological malignancies.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Algate, Paul A., Issaquah, WA, UNITED STATES
Mannion, Jane, Edmonds, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)
US 2004005561 A1 20040108
APPLICATION: US 2002-154884 A1 20020523 (10)
PRIORITY: US 2000-223378P 20000807 (60)
US 2000-223416P 20000804 (60)
US 2000-222903P 20000803 (60)
US 2000-218950P 20000714 (60)
US 2000-206201P 20000522 (60)
US 2000-202084P 20000504 (60)
US 2000-200999P 20000501 (60)
US 2000-200303P 20000428 (60)
US 2000-200779P 20000428 (60)
US 2000-200545P 20000427 (60)
US 2000-190479P 20000317 (60)
US 2000-186126P 20000301 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are methods and compositions for the detection, diagnosis, prognosis, and therapy of hematological malignancies, and in particular, B cell leukemias, lymphomas and multiple myelomas. Disclosed are

compositions, methods and kits for stimulating immune and T cell responses to specific malignancy-related antigenic **polypeptides** and antigenic **polypeptide** fragments thereof in an animal. Also disclosed are compositions and methods for use in the identification of cells and biological samples containing one or more hematological malignancy-related compositions, and methods for the detection and diagnosis of such diseases and affected cell types. Also disclosed are diagnostic and therapeutic kits, as well as methods for the diagnosis, therapy and/or prevention of a variety of leukemias and lymphomas.

CLM What is claimed is:

1. An isolated polynucleotide encoding a protein less than about 550 amino acids, the nucleotides comprising a sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOs:11,002-11,034; (b) sequences having at least 90% identity to the sequences of SEQ ID NOs: 11,002-11,034.

2. An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of: (a) sequences encoded by a polynucleotide of claim 1; and (b) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1; and (c) sequences provided in SEQ ID NOs:11,040-11,056, 11,061-11,177, 11,186-11,189, 11,192, 11,193 and 11,214-11,287.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a **polypeptide** of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample from the patient with a binding agent that binds to a **polypeptide** of claim 2; (b) detecting in the sample an amount of **polypeptide** that binds to the binding agent; and (c) comparing the amount of **polypeptide** to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one **polypeptide** according to claim 2.

8. An oligonucleotide that hybridizes to nucleotides 1-349 of the sequence recited in SEQ ID NO:11,016 under moderately stringent conditions.

9. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of: (a) **polypeptides** provided in SEQ ID NOs:11,040-11,056, 11,061-11,177, 11,186-11,189, 11,192, 11,193 and 11,214-11,287; (b) antigen-presenting cells that express a **polypeptide** according to claim 2, under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

10. An isolated T cell population, comprising T cells prepared according to the method of claim 9.

11. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of: (a) **polypeptides** according to claim 2; (b) polynucleotides according to claim 1; (c) antibodies according to claim 5; (d) fusion proteins according to claim 7; (e) T cell populations according to claim 10; and antigen presenting cells that express a **polypeptide** according to claim 2.

12. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 11.

13. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 11.

14. A method for determining the presence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample from the patient with an oligonucleotide according to claim 8; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

15. A diagnostic kit comprising at least one oligonucleotide according to claim 8.

16. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

17. A method for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) **polypeptides** according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a **polypeptide** of claim 2, such that T cell proliferate; (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

L12 ANSWER 4 OF 38 USPATFULL on STN
2004:2090 Atherosclerosis vaccine.
Hansson, Goran, Stockholm, SWEDEN
Stemme, Sten, Lidingo, SWEDEN
Nicoletti, Antonio, Paris, FRANCE
Wuttge, Dirk, Sundbyberg, SWEDEN
US 2004002111 A1 20040101
APPLICATION: US 2002-221573 A1 20021219 (10)
WO 2001-SE570 20010315
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an antigenic composition capable of eliciting antibodies by interacting with αβ chains of a **T cell receptor** (**TcR**), which composition is comprised of a **peptide**-aldehyde conjugate. The aldehyde portion may be a dialdehyde, such as malondialdehyde (MDA), or a monoaldehyde, such as 4-hydroxynonenal (4-HNE), while the **peptide** portion preferably comprises at least one lysine residue. The antigenic composition according to the invention is capable of recognizing and interacting with a **TcR** having a **complementarity-determining region** 3 (CDR3) of α10 and β6 chains that comprises a cluster of charged and polar amino acids. The invention also relates to a method of producing a vaccine against atherosclerosis by screening of a library of candidate compounds for their ability to bind to a conjugate of oxidized LDL and a dialdehyde as well as to such a vaccine as such.

CLM What is claimed is:
1. An antigenic composition comprised of a **peptide**, which is derived from the protein apoB100, conjugated with an aldehyde, and capable of eliciting an immune response against non-native, oxidized low density lipoprotein (LDL) in a subject by interacting with T cell antigen receptors (TrR).

2. A composition according to claim 1, wherein the aldehyde is an

oxidatively produced aldehyde.

3. A composition according to claim 1 or 2, wherein the aldehyde is a dialdehyde, such as malondialdehyde (MDA).

4. A composition according to claim 1 or 2, wherein the aldehyde is a modified monoaldehyde, such as 4-hydroxynonenal (4-HNE).

5. A composition according to any one of the preceding claims, wherein the **peptide** comprises at least one lysine residue.

6. A composition according to any one of the preceding claims, wherein the **peptide** contains amino acid residues that promote the formation of a polyproline-like structure.

7. A composition according to any one of the preceding claims, the antigenic properties of which is enhanced by association with a major histocompatibility (MHC) class II antigen.

8. A composition according to any one of the preceding claims, wherein the **complementarity-determining region** 3 (CDR3) of said **TcR** comprises a cluster of amino acids the spatial configuration of which enables binding of the **peptide**-aldehyde conjugate.

9. A composition according to any one of the preceding claims, wherein said **TcR** chains are α10 and β6 chains essentially of the sequence disclosed in SEQ ID NO:4 and SEQ ID NO:2, respectively, or an antigenic derivative, fragment or analogue thereof, or a **TcR** that contains a CDR3 region with high structural or conformational homology to said **TcR**.

10. An immunogenic cell, which has been induced to carry MDA-protein conjugates.

11. A method of generating an MHC class II molecule corresponding to a predetermined haplotype, which method comprises expression of **peptide** in a suitable expression system and subsequently conjugation of the expression product to an aldeyde, such as MDA or 4-HNE.

12. A method according to claim 11, wherein said molecule has been compartmentalized in a lipid-protein particle, such as a liposome.

13. A composition according to any one of claims 1-9, a cell according to claim 10 or a molecule generated according to the method of claim 11 or 12 for use as a vaccine.

14. Use of a **peptide** derived from the protein apoB100 conjuated with an aldehyde, which conjugate is capable of eliciting an immune response against non-native, oxidized low density lipoprotein (LDL) in a subject by interacting with T cell antigen receptors (**TcR**), in the manufacture of a vaccine against atherosclerosis.

15. Use of a cell according to claim 10 or a molecule generated according to the method of claim 11 or 12 in the manufacture of a vaccine against atherosclerosis.

16. A method of producing a vaccine against atherosclerosis, which comprises the steps of (a) providing a library of **peptides** derived from the protein apoB100; (b) incubating said **peptides** with aldehydes to produce conjugates of **peptide**-aldehyde; (c) separating non-conjugated **peptides** and aldehydes from the library; (d) incubating the conjugates obtained from step (c) with a **TcR** carrying cell line that react with an oxidized LDL in combination with an antigen-presenting cell that displays MHC class II proteins essentially identical with the cell line; (e) formulating a vaccine composition of conjugates obtained according to step (d) and a pharmaceutically

acceptable carrier.

17. A method of producing a vaccine against atherosclerosis, which comprises the steps of (a) providing a library of **peptides** derived from the protein apoB100; (b) incubating said **peptides** with aldehydes to produce conjugates or **peptide**-aldehyde; (c) separating non-conjugated **peptides** and aldehydes from the library; (d) incubating the conjugates obtained from step (c) with a panel of MHC class II proteins; (e) selecting conjugates capable of binding to the MHC class II proteins corresponding to the MHC haplotype of the individual to be vaccinated; (f) formulating a vaccine composition of conjugates selected according to step (e) and a pharmaceutically acceptable carrier.

18. A method of producing a vaccine against atherosclerosis according to claim 17, wherein the panel of MHC class II proteins consist of soluble oligomers of such proteins produced in a suitable expression system.

19. A method of producing a vaccine against atherosclerosis according to claim 17, wherein the panel of MHC class II proteins is arranged in membrane-like devices.

20. A method according to any one of claims 16-19, wherein the aldehyde is an oxidatively produced aldehyde.

21. A method according to any one of claims 16-20, wherein the aldehyde is a dialdehyde, such as malondialdehyde (MDA).

22. A method according to any one of claims 16-20, wherein the aldehyde is a modified monoaldehyde, such as 4-hydroxynonenal (4-HNE).

23. A method according to any one of claims 16-22, wherein the **peptide** comprises at least one lysine residue.

24. A method according to any one of claims 16-23, wherein the **peptide** contains amino acid residues that promote the formation of a polyproline-like structure.

25. A method according to any one of claims 16-24, wherein the **complementarity-determining region** 3 (CDR3) of the **TcR** of the T cell hybridoma comprises a cluster of amino acids which permit the binding of **peptide**-aldehyde conjugate.

26. A method according to any one of claims 16-25, wherein said **TcR** chains are α10 and β6 chains essentially of the sequence disclosed in SEQ ID NO:4 and SEQ ID NO:2, respectively, or an antigenic derivative, fragment or analogue thereof.

27. A method according to any one of claims 16-26, wherein the vaccine is prepared in a form suitable for subcutaneous injection or nasal, oral/tablet or inhalation administration.

28. A vaccine for generating an immune response in a mammal, such as a human being, to non-native, oxidized LDL, which composition is produced by the method according to any one of claims 16-27 or comprises a composition as defined in any one of claims 1-9, a cell according to claim 10 or a molecule generated according to the method of claim 11 or 12 together with a pharmaceutically acceptable carrier and/or optionally one or more suitable adjuvants.

29. A vaccine according to claim 28, which is in a form suitable for subcutaneous injection or nasal, oral/tablet or inhalation administration.

30. Use of a **T cell receptor** (**TcR**) comprising an amino acid sequence essentially as defined by SEQ ID NO;4 and SEQ ID NO:2, or a

functional derivative, fragment or analogue thereof, as a lead compound in a method of molecular modelling of a ligand capable of binding said **TcR**, said three dimensional structure being characterised by a flattened surface and the presence of exposed surface charges.

31. A method for diagnosis of affliction with atherosclerosis in a patient, by which method the presence of a T cells that recognize oxidized LDL is detected, said method comprising the steps of: (a) providing a sample of body fluid obtained from said patient; (b) combining said sample with a composition as defined in any one of claims 1-9, a cell according to claim 10, a molecule generated according to the method of claim 11 or 12 or an aldehyde-**peptide** conjugate produced according to any one of claims 16-27; (c) detecting the relative presence in said sample of T cells that are activated by exposure to said aldehyde-**peptide** conjugate; (d) comparing the detected presence of T cells in a reference value; and (e) using the comparison in (d) in the diagnosis of affliction with atherosclerosis.

32. A method according to claim 31, wherein in step (d), the proportion of the total amount of T cells which constitutes TcRs comprising an amino acid sequence essentially as defined by SEQ ID NO:4 and SEQ ID NO:2, is determined.

33. A method according to claim 31 or 32, wherein said body fluid sample is a blood or cell sample.

34. A method according to any one of claims 31-33, wherein said marker is an antibody, preferably a monoclonal antibody.

L12 ANSWER 5 OF 38 USPATFULL on STN
2004:2048 Compositions and methods for the detection, diagnosis and therapy of hematological malignancies.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Algate, Paul A., Issaquah, WA, UNITED STATES
Mannion, Jane, Edmonds, WA, UNITED STATES
Clapper, Jonathan David, Seattle, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Ordonez, Nadia, Seattle, WA, UNITED STATES
Carter, Lauren, Seattle, WA, UNITED STATES
McNeill, Patricia Dianne, Federal Way, WA, UNITED STATES
Corixa Corporation, Seattle, WA (U.S. corporation)
US 2004002068 A1 20040101
APPLICATION: US 2002-57475 A1 20020122 (10)
PRIORITY: JP 2001-20745 20010129
WO 2001-US7272 20010301
US 2000-223378P 20000807 (60)
US 2000-223416P 20000804 (60)
US 2000-222903P 20000803 (60)
US 2000-218950P 20000714 (60)
US 2000-206201P 20000522 (60)
US 2000-202084P 20000504 (60)
US 2000-200999P 20000501 (60)
US 2000-200303P 20000428 (60)
US 2000-200779P 20000428 (60)
US 2000-200545P 20000427 (60)
US 2000-190479P 20000317 (60)
US 2000-186126P 20000301 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are methods and compositions for the detection, diagnosis, prognosis, and therapy of hematological malignancies, and in particular, B cell leukemias, lymphomas and multiple myelomas. Disclosed are compositions, methods and kits for eliciting immune and T cell responses to specific malignancy-related antigenic **polypeptides** and antigenic **polypeptide** fragments thereof in an animal. Also disclosed are

compositions and methods for use in the identification of cells and biological samples containing one or more hematological malignancy-related compositions, and methods for the detection and diagnosis of such diseases and affected cell types. Also disclosed are diagnostic and therapeutic kits, as well as methods for the diagnosis, therapy and/or prevention of a variety of leukemias and lymphomas.

CLM What is claimed is:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of: (a) the sequences provided in SEQ ID NOs:10,486-10,536; SEQ ID NOs:10,537-10,580; SEQ ID NOs:10,581-10,596; SEQ ID NO:10,597; SEQ ID NO:10,845; SEQ ID NO:10,846; SEQ ID NO:10,970; SEQ ID NO:10,971; SEQ ID NO:10,972; SEQ ID NO:10,973; and SEQ ID NO:10,974; (b) complements of any of the sequences provided in SEQ ID NOs:10,486-10,536; SEQ ID NOs:10,537-10,580; SEQ ID NOs:10,581-10,596; SEQ ID NO:10,597; SEQ ID NO:10,845; SEQ ID NO:10,846; SEQ ID NO:10,970; SEQ ID NO:10,971; SEQ ID NO:10,972; SEQ ID NO:10,973; and SEQ ID NO:10,974; (c) sequences having at least 90% identity to any one of the sequences provided in SEQ ID NOs:10,486-10,536; SEQ ID NOs:10,537-10,580; SEQ ID NOs:10,581-10,596; SEQ ID NO:10,597; SEQ ID NO:10,845; SEQ ID NO:10,846; SEQ ID NO:10,970; SEQ ID NO:10,971; SEQ ID NO:10,972; SEQ ID NO:10,973; and SEQ ID NO:10,974; and (d) degenerate variants of any one of the sequences provided in SEQ ID NOs:10,486-10,536; SEQ ID NOs:10,537-10,580; SEQ ID NOs:10,581-10,596; SEQ ID NO:10,597; SEQ ID NO:10,845; SEQ ID NO:10,846; SEQ ID NO:10,970; SEQ ID NO:10,971; SEQ ID NO:10,972; SEQ ID NO:10,973; and SEQ ID NO:10,974.

2 An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of: (a) sequences encoded by a polynucleotide of claim 1; and (b) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a **polypeptide** of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of: (a) obtaining a biological sample from the patient; (b) contacting the biological sample with a binding agent that binds to a **polypeptide** of claim 2; (c) detecting in the sample an amount of **polypeptide** that binds to the binding agent; and (d) comparing the amount of **polypeptide** to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one **polypeptide** according to claim 2.

8. The fusion protein of claim 7, further comprising Ra12.

9. The fusion protein of claim 7, further comprising a His tag.

10. An oligonucleotide that hybridizes to the polynucleotides of claim 1.

11. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of: (a) **polypeptides** according to claim 2; (b) polynucleotides according to claim 1; and (c) antigen-presenting cells that express a **polypeptide** according to claim 1, under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

12. An isolated T cell population, comprising T cells prepared according to the method of claim 11.

13. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of: (a) **polypeptides** according to claim 2; (b) polynucleotides according to claim 1; (c) antibodies according to claim 5; (d) fusion proteins according to claim 7; (e) T cell populations according to claim 12; and (f) antigen presenting cells that express a **polypeptide** according to claim 2.

14. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 13.

15. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 13.

16. A method for determining the presence of a cancer in a patient, comprising the steps of: (a) obtaining a biological sample from the patient; (b) contacting the biological sample with an oligonucleotide according to claim 10; (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and (d) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

17. A diagnostic kit comprising at least one oligonucleotide according to claim 10.

18. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

19. A method for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) **polypeptides** according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a **polypeptide** of claim 2, such that T cell proliferate; (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

20. An isolated polynucleotide comprising a sequence selected from the group consisting of: (a) sequence provided in SEQ ID NO:10,469 or SEQ ID NO:10,470; (b) complements of the sequence provided in SEQ ID NO: 10,469 or SEQ ID NO: 10,470; (c) sequences having at least 90% identity to SEQ ID NO:10,469 or SEQ ID NO:10,470; and (d) degenerate variants of SEQ ID NO: 10,469 or SEQ ID NO: 10,470.

21. An isolated **polypeptide** comprising an amino acid sequence provided in SEQ ID NO:10,471 or SEQ ID NO:10,474.

22. An isolated polynucleotide comprising a sequence selected from the group consisting of: (a) sequence provided in SEQ ID NO:10,480; (b) complements of the sequence provided in SEQ ID NO: 10,480; (c) sequences having at least 90% identity to a sequence of SEQ ID NO: 10,480; and (d) degenerate variants of a sequence provided in SEQ ID NO: 10,480.

23. An isolated **polypeptide** comprising an amino acid sequence of SEQ ID NO:10,481.

24. An isolated **polypeptide** comprising an amino acid sequence selected

from the group consisting of: (a) sequences encoded by a polynucleotide of claim 20 or 22; and (b) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 20 or 22.

25. An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in any one of SEQ ID NOs:10,599-10,819; and (b) sequences provided in anyone of SEQ ID NOs:10,820-10,842.

26. An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in any one of SEQ ID NOs: 10,849-10,908; and (b) sequences provided in any one of SEQ ID NOs:10,909-10,968.

L12 ANSWER 6 OF 38 USPATFULL on STN
2003:334682 Compositions and methods for WT1 specific immunotherapy.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Cheever, Martin A., Mercer Island, WA, UNITED STATES
Corixa Corporation, Seattle, WA (U.S. corporation)
US 2003235557 A1 20031225
APPLICATION: US 2002-244830 A1 20020916 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compositions comprise one or more of a WT1 polynucleotide, a WT1 **polypeptide**, an antigen-presenting cell presenting a WT1 **polypeptide**, an antibody that specifically binds to a WT1 **polypeptide**; or a T cell that specifically reacts with a WT1 **polypeptide**. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.

CLM What is claimed is:

1. A method for inducing an immune response in an animal, comprising: (a) administering to said animal a first composition comprising a first viral vector wherein said first viral vector comprises at least an immunogenic portion of a WT1 polynucleotide operably linked to an expression control sequence; (b) administering to said animal a second composition comprising a second viral vector wherein said second viral vector comprises at least an immunogenic portion of a WT1 polynucleotide operably linked to an expression control sequence; and thereby inducing an immune response in the animal.

2. The method of claim 1 wherein said first viral vector comprises a recombinant vaccinia vector.

3. The method of claim 1 wherein said first viral vector comprises rV-WT1/TRICOM.

4. The method of claim 1 wherein said second viral vector comprises a recombinant fowlpox vector.

5. The method of claim 1 wherein said second viral vector comprises rF-WT1/TRICOM.

6. The method of claim 1 wherein said first and said second viral vectors further comprise at least one polynucleotide encoding a costimulatory molecule.

7. The method of claim 6 wherein said costimulatory molecule is selected from the group consisting of B7-1, ICAM-1, and LFA-3.

8. The method of claim 1 wherein said first composition is administered at a first timepoint and said second composition is administered subsequently at a second and a third timepoint.

9. An expression vector comprising at least an immunogenic portion of a

wit polynucleotide operably linked to an expression control sequence.

10. An expression vector according to claim 9 wherein said vector comprises a baculovirus expression vector.

11. An expression vector according to claim 9 wherein said vector comprises a fowlpox vector.

12. An expression vector according to claim 9 wherein said vector comprises a vaccinia vector.

13. A host cell transformed or transfected with an expression vector according to any one of claims 9-12.

L12 ANSWER 7 OF 38 USPATFULL on STN
2003:318635 Novel nucleic acids and **polypeptides**.
Tang, Y. Tom, San Jose, CA, UNITED STATES
Yang, Yonghong, San Jose, CA, UNITED STATES
Wang, Zhiwei, Sunnyvale, CA, UNITED STATES
Weng, Gezhi, Piedmont, CA, UNITED STATES
Ma, Yunqing, Santa Clara, CA, UNITED STATES
US 2003224379 A1 20031204
APPLICATION: US 2002-243552 A1 20020912 (10)
PRIORITY: WO 2001-US2623 20010125
WO 2001-US3800 20010205
WO 2001-US4927 20010226
WO 2001-US4941 20010305
WO 2001-US8631 20010330
WO 2001-US8656 20010416
WO 2001-US14827 20010516
US 2001-322511P 20010913 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides novel nucleic acids, novel **polypeptide** sequences encoded by these nucleic acids and uses thereof.
CLM What is claimed is:
1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-337.

2. An isolated polynucleotide encoding a **polypeptide** with biological activity, wherein said polynucleotide hybridizes to the polynucleotide of claim 1 under stringent hybridization conditions.

3. An isolated polynucleotide encoding a **polypeptide** with biological activity, wherein said polynucleotide has greater than about 99% sequence identity with the polynucleotide of claim 1.

4. The polynucleotide of claim 1 wherein said polynucleotide is DNA.

5. An isolated polynucleotide of claim 1 wherein said polynucleotide comprises the complementary sequences.

6. A vector comprising the polynucleotide of claim 1.

7. An expression vector comprising the polynucleotide of claim 1.

8. A host cell genetically engineered to comprise the polynucleotide of claim 1.

9. A host cell genetically engineered to comprise the polynucleotide of claim 1 operatively associated with a regulatory sequence that modulates expression of the polynucleotide in the host cell.

10. An isolated **polypeptide**, wherein the **polypeptide** is selected from the group consisting of: (a) a **polypeptide** encoded by any one of

the polynucleotides of claim 1, and (b) a **polypeptide** encoded by a polynucleotide hybridizing under stringent conditions with any one of SEQ ID NO: 1-337.

11. A composition comprising the **polypeptide** of claim 10 and a carrier.

12. An antibody directed against the **polypeptide** of claim 10.

13. A method for detecting the polynucleotide of claim 1 in a sample, comprising: a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form the complex; and b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected.

14. A method for detecting the polynucleotide of claim 1 in a sample, comprising: a) contacting the sample under stringent hybridization conditions with nucleic acid primers that anneal to the polynucleotide of claim 1 under such conditions; b) amplifying a product comprising at least a portion of the polynucleotide of claim 1; and c) detecting said product and thereby the polynucleotide of claim 1 in the sample.

15. The method of claim 14, wherein the polynucleotide is an RNA molecule and the method further comprises reverse transcribing an annealed RNA molecule into a cDNA polynucleotide.

16. A method for detecting the **polypeptide** of claim 10 in a sample, comprising: a) contacting the sample with a compound that binds to and forms a complex with the **polypeptide** under conditions and for a period sufficient to form the complex; and b) detecting formation of the complex, so that if a complex formation is detected, the **polypeptide** of claim 10 is detected.

17. A method for identifying a compound that binds to the **polypeptide** of claim 10, comprising: a) contacting the compound with the **polypeptide** of claim 10 under conditions sufficient to form a **polypeptide**/compound complex; and b) detecting the complex, so that if the **polypeptide**/compound complex is detected, a compound that binds to the **polypeptide** of claim 10 is identified.

18. A method for identifying a compound that binds to the **polypeptide** of claim 10, comprising: a) contacting the compound with the **polypeptide** of claim 10, in a cell, under conditions sufficient to form a **polypeptide**/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and b) detecting the complex by detecting reporter gene sequence expression, so that if the **polypeptide**/compound complex is detected, a compound that binds to the **polypeptide** of claim 10 is identified.

19. A method of producing the **polypeptide** of claim 10, comprising, a) culturing a host cell comprising a polynucleotide sequence selected from the group consisting of any of the polynucleotides from SEQ ED NO: 1-337, under conditions sufficient to express the **polypeptide** in said cell; and b) isolating the **polypeptide** from the cell culture or cells of step (a).

20. An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of any one of the **polypeptides** SEQ ID NO: 338-674.

21. The **polypeptide** of claim 20 wherein the **polypeptide** is provided on a **polypeptide** array.

22. A collection of polynucleotides, wherein the collection comprising of at least one of SEQ ID NO: 1-337.

23. The collection of claim 22, wherein the collection is provided on a

nucleic acid array.

24. The collection of claim 23, wherein the array detects full-matches to any one of the polynucleotides in the collection.

25. The collection of claim 23, wherein the array detects mismatches to any one of the polynucleotides in the collection.

26. The collection of claim 22, wherein the collection is provided in a computer-readable format.

L12 ANSWER 8 OF 38 USPATFULL on STN
2003:306026 Compositions and methods for WT1 specific immunotherapy.
Gaiger, Alexander, Seattle, WA, UNITED STATES
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Jaya, Nomalie, Seattle, WA, UNITED STATES
Corixa Corporation, Seattle, WA (U.S. corporation)
US 2003215458 A1 20031120
APPLICATION: US 2002-286333 A1 20021030 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compositions comprise one or more of a WT1 polynucleotide, a WT1 **polypeptide**, an antigen-presenting cell presenting a WT1 **polypeptide**, an antibody that specifically binds to a WT1 **polypeptide**; or a T cell that specifically reacts with a WT1 **polypeptide**. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.
CLM What is claimed is:
1. An isolated **polypeptide** comprising an immunogenic portion of a Wilms' tumor antigen, selected from the group consisting of SEQ ID NOs:478 and 502, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with WT1-specific antisera and/or T-cell lines or clones is not substantially diminished.

2. The isolated **polypeptide** according to claim 1 wherein the immunogenic portion has been modified such that the ability of the immunogenic portion to bind to an MHC molecule is increased relative to that of the immunogenic portion.

3. The isolated **polypeptide** according to claim 2 wherein the immunogenic portion has been modified such that the ability of the immunogenic portion to bind to HLA-A2 is increased relative to that of the unmodified immunogenic portion.

4. An isolated **polypeptide** comprising a Wilms' tumor antigen having a deletion of a proline rich region.

5. An isolated **polypeptide** according to claim 4 wherein said proline rich region is from about amino acid positions 54 to 68 of the Wilms' tumor antigen.

6. The isolated **polypeptide** of claim 5 wherein said **polypeptide** comprises the amino acid sequence set forth in any one of SEQ ID NO:478 and 502.

7. A fusion protein comprising at least one **polypeptide** according to any one of claims 1, 2 or 4.

8. The fusion protein of claim 7 wherein said fusion partner is selected from the group consisting of Ra12, protein D, LYTA, a HIS tag, a targeting signal capable of directing a **polypeptide** to the endosomal/lysosomal compartment, twin arginine translocator, and truncated twin arginine translocator.

9. The fusion protein of claim 8 wherein the fusion protein comprises a twin arginine translocator signal **peptide**.

10. The fusion protein of claim 8 wherein the fusion partner comprises the amino acid sequence of any one of SEQ ID NOs:504 and 506.

11. The fusion protein of claim 10 wherein the fusion protein comprises the amino acid sequence of any one of SEQ ID NOs:470, 479-483, and 499.

12. An isolated polynucleotide encoding the fusion proteins of any one of claims 7, 9, and 11.

13. The isolated polynucleotide of claim 12 wherein the polynucleotide has been codon optimized for expression in E. coli.

14. The isolated polynucleotide of claim 12 wherein the polynucleotide comprises a sequence of any one of SEQ ID NOs: 469, 471, and 472-477 and 503, 505.

15. A composition comprising a **polypeptide** of claim 1, 4, 6, or 11 in combination with a pharmaceutically acceptable carrier or excipient.

16. A vaccine comprising a **polypeptide** of claim 1, 4, 6, or 11 in combination with a non-specific immune response enhancer.

17. The vaccine according to claim 15 wherein the non-specific immune response enhancer preferentially enhances a T cell response in a patient.

18. The vaccine according to claim 15, wherein the immune response enhancer is selected from the group consisting of 3d-MPL, MPL, RC-529, AGP's, Montanide ISA50, Seppic Montanide ISA 720, a cytokine, a microsphere, dimethyl dioctadecyl ammoniumbromide (DDA) based adjuvants, AS-1, AS-2, Ribi Adjuvant system based adjuvant, QS21, saponin based adjuvants, Syntex adjuvant in its microfluidized form, MV, ddMV, immune stimulating complex (iscom) based adjuvants, and inactivated toxins.

19. An expression vector comprising a polynucleotide of claim 12 operably linked to an expression control sequence.

20. A host cell transformed or transfected with an expression vector according to claim 19.

L12 ANSWER 9 OF 38 USPATFULL on STN
2003:282281 Compositions and methods for WT1 specific immunotherapy.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Smithgall, Molly D., Seattle, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Cheever, Martin A., Mercer Island, WA, UNITED STATES
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Sutherland, R. Alec, Bothell, WA, UNITED STATES
Mossman, Sally P., Seattle, WA, UNITED STATES
Evans, Lawrence S., Seattle, WA, UNITED STATES
Swanson, Ryan M., Seattle, WA, UNITED STATES
Corixa Corporation, Seattle, WA, UNITED STATES (U.S. corporation)
US 2003198622 A1 20031023
APPLICATION: US 2002-195835 A1 20020712 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compositions comprise one or more of a WT1 polynucleotide, a WT1 **polypeptide**, an antigen-presenting cell presenting a WT1 **polypeptide**, an antibody that specifically binds to a WT1 **polypeptide**; or a T cell that specifically reacts with a WT1

polypeptide. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.

CLM What is claimed is:

1. A method for inducing an immune response in an animal, comprising: (a) providing a composition comprising a polynucleotide encoding at least an immunogenic portion of a WT1 **polypeptide**, wherein the polynucleotide has at least 90% identity to SEQ ID NO:452, 389, 453, and 381, and (b) administering said composition to the animal; thereby inducing an immune response in the animal.

2. The method of claim 1, wherein said composition further comprises a component selected from the group consisting of a physiologically acceptable carrier and an adjuvant.

3. The method according to claim 1, wherein the WT1 polynucleotide is delivered by a viral based delivery system.

4. The method according to claim 3, wherein the viral based delivery system is an adenovirus.

5. The method according to claim 3, wherein the viral based delivery system is an alphavirus.

6. The method according to claim 1, wherein the WT1 polynucleotide is delivered as a naked DNA.

7. The method of claim 1, wherein the immune response induced is a CD8+ cytotoxic T lymphocyte response.

8. The method of claim 1, wherein the immune response induced is both a CD4+ T helper and CD8+ cytotoxic T cell immune response.

9. A method for treating a malignancy associated with WT1 expression in a patient, comprising administering to the patient a composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component comprising at least an immungenic portion of a WT1 **polypeptide**.

10. An isolated **polypeptide** comprising at least an immunogenic portion of the WT1 protein, wherein said **polypeptide** comprises the amino acid sequence set forth in SEQ ID NO:241.

11. The isolated **polypeptide** according to claim 10 wherein the **polypeptide** has been modified such that the ability of the **polypeptide** to bind to HLA-A2 is increased relative to that of the **polypeptide** set forth in SEQ ID NO:241.

12. The isolated **polypeptide** according to claim 11 wherein said **polypeptide** has increased immunogenicity relative to the **polypeptide** set forth in SEQ ID NO:241.

13. The isolated **polypeptide** according to claim 11 wherein said **polypeptide** comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NOs:414-450.

14. The isolated **polypeptide** according to claim 10 wherein the **polypeptide** has been modified such that the ability of the **polypeptide** to bind to HLA-A2 is increased relative to that of the **polypeptide** set forth in SEQ ID NO:241.

15. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 1 (P1) of SEQ ID NO:241

16. The isolated **polypeptide** according to claim 14 wherein said

modification comprises a substitution at position 2 (P2) of SEQ ID NO:241.

17. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 4 (P4) of SEQ ID NO:241.

18. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 6 (P6) of SEQ ID NO:241.

19. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 8 (P8) of SEQ ID NO:241.

20. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 9 (P9) of SEQ ID NO:241.

21. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 1 (P1) and position 4 (P4) of SEQ ID NO:241.

22. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 1 (P1) and position 9 (P9) of SEQ ID NO:241.

23. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 1 (P1), position 4 (P4), and position 9 (P9) of SEQ ID NO:241.

24. The isolated **polypeptide** according to claim 14 wherein said modification comprises a substitution at position 6 (P6) and position 9 (P9) of SEQ ID NO:241.

25. An isolated **polypeptide** comprising at least an immunogenic portion of a WT1 **polypeptide**, wherein said immunogenic portion comprises an amino acid sequence selected from the group consisting of: (i) a sequence set forth in SEQ ID NO:451; and (ii) a **polypeptide** selected from the group consisting of: (a) a sequence set forth in any one of SEQ ID NOs:414-450; (b) a sequence having at least 70% identity to a sequence set forth in any one of SEQ ID NOs:414-450; and (c) a sequence having at least 90% identity to a sequence set forth in any one of SEQ ID NOs:414-450; wherein the ability of the **polypeptide** to bind to HLA-A2 is increased relative to that of the **polypeptide** set forth in SEQ ID NO:241.

26. A method for inducing an immune response in a mammal, comprising: (a) providing a composition comprising a polynucleotide encoding the isolated **polypeptide** of claim 25; and (b) administering said polynucleotide to the mammal; thereby inducing an immune response in the mammal.

27. An expression vector comprising a polynucleotide of any one of the sequences set forth in SEQ ID NOs:452 and 453 or a polynucleotide encoding the isolated **polypeptide** of claim 25 operably linked to an expression control sequence.

28. A host cell transformed or transfected with an expression vector according to claim 27.

29. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of: (a) a **polypeptide** according to claim 25; (b) antigen-presenting cells pulsed with or that express a **polypeptide** according to claim 26, under conditions and for a time

sufficient to permit the stimulation and/or expansion of T cells.

30. An isolated T cell population, comprising T cells prepared according to the method of claim 29.

31. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of: (a) **polypeptides** according to claim 25; and (b) T cells according to claim 31.

32. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 31.

33. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 32.

34. An isolated **polypeptide** comprising an amino acid sequence of any one of SEQ ID NOs:454-455.

L12 ANSWER 10 OF 38 USPATFULL on STN
2003:271062 Methods of selecting **T cell receptor** V **peptides** for therapeutic use .

Vandenbark, Arthur A., Portland, OR, UNITED STATES
Oregon Health and Science University (U.S. corporation)The Government of the United States of America, dba The Department of Veterans Affairs (U.S. corporation)
US 2003190665 A1 20031009
APPLICATION: US 2003-438729 A1 20030514 (10)
PRIORITY: US 2000-203984P 20000512 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method is disclosed to identify a **T cell receptor** (**TCR**) variable (V) **peptide** of use as a therapeutic agent in a subject. A method is also disclosed for monitoring the efficacy of a **T Cell Receptor** (**TCR**) V **peptide** for the treatment of a subject. In another embodiment, a method is disclosed for selecting a **TCR** V **peptide** of use in therapy for a subject having an autoimmune disease.

CLM What is claimed is:

1. A method of identifying a **T cell receptor** (**TCR**) variable (V) **peptide** of use as a therapeutic agent in a subject affected with a disorder, comprising: a) screening **TCR V beta peptides**, **TCR** V alpha **peptides**, or both **TCR V beta peptides** and **TCR** V alpha **peptides** to select a **TCR** V **peptide** that produces altered expression of a cytokine elicited in response to the **TCR** V **peptide** by T cells from the subject as compared to a control subject; b) determining a regulatory activity of CD4+CD25+ T cells isolated from the subject elicited in response to the **TCR** V **polypeptide**; thereby identifying a **TCR** V **peptide** of use as a therapeutic agent.

2. The method of claim 1, wherein the disorder is an autoimmune disease.

3. The method of claim 2, wherein the autoimmune disease is multiple sclerosis, Rheumatoid arthritis, systemic lupus erythematosis, type I diabetes, non-obese diabetes, myasthenia gravis, Grave's disease, Hashimoto's thyroiditis, or psoriasis.

4. The method of claim 3, wherein the autoimmune disease is multiple sclerosis.

5. The method of claim 1, wherein the method comprises screening **TCR V beta peptides**.

6. The method of claim 1, wherein the method comprises screening **TCR** V alpha **peptides**.

7. The method of claim 1, wherein altered expression of the cytokine is indicated by at least a 50% higher expression of the cytokine by T cells from the subject elicited in response to the **TCR** V **peptide** as compared to expression of the cytokine by T cells from a control subject elicited in response to the **TCR** V **peptide**.

8. The method of claim 1, wherein altered expression of the cytokine is indicated by at least a 50% lower expression of the cytokine by T cells from the subject elicited in response to the **TCR** V **peptide** as compared to expression of the cytokine by T cells from a control subject elicited in response to the **TCR** V **peptide**.

9. The method of claim 1, wherein the cytokine is an anti-inflammatory cytokine.

10. The method of claim 9, wherein the anti-inflammatory cytokine is interleukin-10 (IL-10).

11. The method of claim 9, wherein the anti-inflammatory cytokine is interferon gamma (IFN-γ).

12. The method of claim 1, wherein expression of the cytokine is determined by an immunospot assay.

13. The method of claim 1, wherein the **TCR** V **peptide** is a CDR2 **peptide**.

14. The method of claim 1, wherein determining the regulatory activity of the CD4+CD25+ T cells comprises contacting CD4+ T cells with the **TCR** V **peptide** to produce regulatory CD4+CD25+ T cells; contacting the regulatory CD4+CD25+ T cells with CD4+CD25- indicator T cells; and determining the proliferation of the CD4+CD25- indicator T cells or the release of inflammatory cytokines by the CD4+CD25- indicator cells after stimulation of a **T cell receptor** on the CD4+CD25- indicator cells.

15. The method of claim 14, wherein the stimulation of the **T cell receptor** comprises contacting the CD4+CD25- indicator cells with an antibody that specifically binds CD3 and an antibody that specifically binds CD28 or contacting the CD4+CD25- cells with a specific antigen.

16. The method of claim 14, wherein a decrease in the proliferation of the CD4+CD25- indicator T cells as compared to a control indicates that the **TCR** V **peptide** elicits regulatory activity.

17. A method of monitoring the efficacy of a **T Cell Receptor** (**TCR**) V **peptide** for the treatment of a subject, comprising: exposing CD4+ cells from the subject to the **TCR** V **peptide**; and determining a T cell regulatory activity of CD4+CD25+ T cells isolated from the subject, wherein induction of regulatory activity indicates the efficacy of the **TCR** V **peptide** for the treatment of the subject.

18. The method of claim 17, wherein the subject has an autoimmune disease.

19. The method of claim 18, wherein the autoimmune disease is multiple sclerosis, Rheumatoid arthritis, systemic lupus erythematosis, type I diabetes, non-obese diabetes, myasthenia gravis, Grave's disease, Hashimoto's thyroiditis, or psoriasis.

20. The method of claim 19, wherein the autoimmune disease is multiple sclerosis.

21. The method of claim 18, wherein the **TCR** V **peptide** is a **TCR V beta peptide**.

22. The method of claim 18, wherein the **TCR** V **peptide** is a **TCR** V alpha **peptide**.

23. The method of claim 18, wherein the **TCR** V **peptide** is a CDR2 **peptide**.

24. The method of claim 18, wherein determining the regulatory activity of the CD4+CD25+ T cells comprises contacting CD4+ T cells with the **TCR** V **peptide** to produce regulatory CD4+CD25+ T cells; contacting the regulatory CD4+CD25+ T cells with CD4+CD25- indicator T cells; and determining the proliferation of the CD4+CD25- indicator T cells or the release of inflammatory cytokines by the CD4+CD25- indicator cells after stimulation of a **T cell receptor** on the CD4+CD25- indicator cells.

25. The method of claim 24, wherein the stimulation of the **T cell receptor** comprises contacting the CD4+CD25- indicator cells with an antibody that specifically binds CD3 and an antibody that specifically binds CD28 or contacting the CD4+CD25- cells with a specific antigen.

26. The method of claim 23, wherein a decrease in the proliferation of the CD4+CD25- indicator T cells as compared to a control indicates that the **TCR** V **peptide** elicits regulatory activity.

27. A method of selecting a therapy for a subject having an autoimmune disease, comprising: a) identifying a **T Cell Receptor** Variable (**TCR** V) gene expressed by target T cells in the subject by screening for expression of a **TCR** V genes by activated T cells from the subject; and determining expression of a cytokine elicited in response to one or more **TCR** V **peptides** corresponding to the **TCR** V gene by T cells from the subject, thereby identifying a **TCR** V gene expressed by target T cells; and b) identifying a **TCR** V **peptides** corresponding to the **TCR** V gene that elicit T cell regulatory activity by a T cell isolated from the subject; thereby selecting a therapy that targets T cells expressing the **TCR** V gene.

28. The method of claim 27, wherein the T cells are CD4+CD25+ T cells.

29. The method of claim 27, wherein the **TCR** V **peptides** are **TCR V beta peptides**.

30. The method of claim 27, wherein the **TCR** V **peptides** are **TCR** V alpha **peptides**.

31. The method of claim 27, wherein the **TCR** V **peptides** are CDR2 **peptides**.

32. The method of claim 27, wherein identifying the **TCR** V **peptide** corresponding to the **TCR** V gene that elicits T cell regulatory activity by a T cell isolated from the subject comprises contacting CD4+ T cells with the **TCR** V **peptide** to produce regulatory CD4+CD25+ T cells; contacting the regulatory CD4+CD25+ T cells with CD4+CD25- indicator T cells; and determining the proliferation of the CD4+CD25- indicator T cells or the release of inflammatory cytokines by the CD4+CD25- indicator cells after stimulation of a **T cell receptor** on the CD4+CD25- indicator cells.

33. The method of claim 32, wherein the stimulation of the **T cell receptor** comprises contacting the CD4+CD25- indicator cells with an antibody that specifically binds CD3 and an antibody that specifically binds CD28 or contacting the CD4+CD25- cells with a specific antigen.

34. The method of claim 32, wherein a decrease in the proliferation of the CD4+CD25- indicator T cells as compared to a control indicates that the **TCR** V **peptide** elicits regulatory activity.

35. The method of claim 32, wherein the subject has an autoimmune

disease.

36. The method of claim 35, wherein the autoimmune disease is multiple sclerosis, Rheumatoid arthritis, systemic lupus erythematosis, type I diabetes, non-obese diabetes, myasthenia gravis, Grave's disease, Hashimoto's thyroiditis, or psoriasis.

37. The method of claim 35, wherein the autoimmune disease is multiple sclerosis.

L12 ANSWER 11 OF 38 USPATFULL on STN
2003:251620 Method of treating immune pathologies with low dose estrogren.
Offner, Halina, Portland, OR, UNITED STATES
US 2003176409 A1 20030918
APPLICATION: US 2002-275833 A1 20021108 (10)
WO 2001-US40710 20010511
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a method of ameliorating a **Th1**-mediated immune pathology in a mammal. The method is practiced by administering a low dose of estrogen to the mammal. Optionally, an immunotherapeutic agent can also be administered to the mammal. Also provided are kits containing a low dose of estrogen and an immunotherapeutic agent.

CLM What is claimed is:

1. A method of ameliorating a **Th1**-mediated immune pathology in a mammal, comprising administering a low dose of estrogen to said mammal.

2. The method of claim 1, wherein said **Th1**-mediated immune pathology is an autoimmune pathology.

3. The method of claim 2, wherein said autoimmune pathology is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and psoriasis.

4. The method of any of claims 1-3, wherein said mammal is female.

5. The method of any of claims 1-3, wherein said mammal is male.

6. The method of any of claims 1-5, wherein said mammal is a human.

7. The method of any of claims 1-6, wherein said estrogen is selected from the group consisting of 17β-estradiol, estriol and estrone.

8. The method of claim 7, wherein said estrogen is 17β-estradiol.

9. The method of any of claims 1-8, wherein said low dose of estrogen is an amount sufficient to raise the serum concentration of estrogen in said mammal to within the range from 30 pg/ml to 1000 pg/ml.

10. The method of any of claims 1-8, wherein said low dose of estrogen is an amount sufficient to raise the serum concentration of estrogen in said mammal to within the range from 50 pg/ml to 500 pg/ml.

11. The method of any of claims 1-8, wherein said low dose of estrogen is an amount sufficient to raise the serum concentration of estrogen to within the range from 100 pg/ml to 250 pg/ml.

12. The method of any of claims 1-11, wherein said estrogen is administered by a route selected from oral, transdermal, respiratory, subcutaneous and intravenous routes.

13. The method of any of claims 1-12, wherein said amelioration is apparent by magnetic resonance imaging.

14. The method of any of claims 1-13, further comprising administering

an immunotherapeutic agent to said mammal.

15. The method of claim 14, wherein said immunotherapeutic agent is an immunomodulatory agent.

16. The method of claim 15, wherein said immunomodulatory agent is a **peptide** selected from the group consisting of an antigen **peptide**, an HLA **peptide**, a **T cell receptor peptide** and an analog of any of said **peptides** that induces substantially the same immune response as said **peptide**.

17. The method of claim 16, wherein said immunomodulatory agent is a **T cell receptor peptide** or an analog thereof that induces substantially the same immune response as said **T cell receptor peptide**.

18. The method of claim 17, wherein said **T cell receptor peptide** comprises an amino acid sequence selected from the group consisting of human **v**β2, **v**β3, **v**β5.1, **v**β5.2, **v**β6.1, **v**β6.5, **v**β7, **v**β13, **v**β14 and **v**β17 amino acid sequences.

19. The method of claim 16, wherein said **T cell receptor peptide** comprises at least a part of a CDR2 region.

20. The method of claim 15, wherein said immunomodulatory agent is an expressible nucleic acid molecule that encodes a **peptide** selected from the group consisting of an antigen **peptide**, an HLA **peptide**, a **T cell receptor peptide** and an analog of any of said **peptides** that induces substantially the same immune response as said **peptide**.

21. The method of claim 14, wherein said immunotherapeutic agent is an immunoblocking agent.

22. The method of claim 21, wherein said immunoblocking agent specifically binds a molecule selected from the group consisting of a **T cell receptor**, an antigen and a HLA molecule.

23. The method of claim 22, wherein said immunoblocking agent specifically binds a **T cell receptor** variable chain selected from the group consisting of human **v**β2, **v**β3, **v**β5.1, **v**β5.2, **v**β6.1, **v**β6.5, **v**β7, **v**β13, **v**β14 and **v**β17.

24. The method of claim 21, wherein said immunoblocking agent is an antibody.

25. The method of claim 21, wherein said immunoblocking agent is attached to a toxic moiety.

26. The method of claim 21, wherein said immunoblocking agent is an altered **peptide** ligand.

27. The method of claim 15, wherein said immunotherapeutic agent specifically binds a **Th1** cytokine.

28. The method of claim 27, wherein said **Th1** cytokine is tumor necrosis factor alpha.

29. The method of claim 15, wherein said immunotherapeutic agent is a purine analog.

30. The method of claim 15, wherein said immunotherapeutic agent is glatiramer acetate.

31. The method of claim 15, wherein said immunotherapeutic agent is a

cytokine.

32. The method of claim 31, wherein said cytokine is selected from the group consisting of IFNβ-1a and IFNβ-1b.

33. A kit, comprising a low dose of estrogen and an immunotherapeutic agent, wherein administration of said low dose of estrogen and said immunotherapeutic agent ameliorates a **Th1**-mediated immune pathology in a mammal.

L12 ANSWER 12 OF 38 USPATFULL on STN
2003:225302 Compositions and methods for treatment of neoplastic disease.
Terman, David S., Pebble Beach, CA, UNITED STATES
US 2003157113 A1 20030821
APPLICATION: US 2000-751708 A1 20001228 (9)
PRIORITY: US 1999-173371P 19991228 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention comprises compositions and methods for treating a tumor or neoplastic disease in a host, The methods employ conjugates comprising superantigen **polypeptides**, nucleic acids with other structures that preferentially bind to tumor cells and are capable of inducing apoptosis. Also provided are superantigen-glycolipid conjugates and vesicles that are loaded onto antigen presenting cells to activate both T cells and NKT cells. Cell-based vaccines comprise tumor cells engineered to express a superantigen along with glycolipids products which, when expressed, render the cells capable of eliciting an effective anti-tumor immune response in a mammal into which these cells are introduced. Included among these compositions are tumor cells, hybrid cells of tumor cells and accessory cells, preferably dendritic cells. Also provided are tumoricidal T cells and NKT cells devoid of inhibitory receptors or inhibitory signaling motifs which are hyperresponsive to the the above compositions and lipid-based tumor associated antigens that can be administered for adoptive immunotherapy of cancer and infectious diseases.

CLM What is claimed is:

1. A receptor in a mammalian cell useful in the treatment of cancer which inhibits cellular activation by receptors specific for lipid-based tumor associatiated antigens.

2 The receptor of claim 1 wherein the lipid antigen is a bacterial, fungal, protozoal or mycobacterial antigen.

3. The inhibitory receptor of claims 1 and 2 wherein said inhibitory receptor contains an inhibitory receptor tyrosine-based inhibitory motifs (ITIMs).

4. The inhibitory receptor of claim 1, 2 wherein said receptor is specific for lipid-based tumor associated antigen and/or self MHC or CD1 molecules.

5. A receptor in a mammalian cell wherein said receptor inhibits cellular activation by receptors specific for lipid-based infectious disease associated antigens derived from bacteria, fungi, mycobacterium, parasite, virus, eukaryote or prokaryote antigens in the context of MHC or CD1.

6. A mammalian cell useful in the treatment of cancer wherein the inhibitory receptor for lipid-based tumor associated antigens is deleted or functionally deactivated.

7. A mammalian cell useful in the treatment of cancer wherein inhibitory receptor tyrosine-based inhibitory motifs of the inhibitory receptor for lipid-based tumor associated antigens are deleted or functionally deactivated.

8. A mammalian cell useful in the treatment of cancer wherein the the inhibitory receptor for superantigens associated with self antigens are functionally deleted.

9. A mammalian cell useful in the treatment of cancer wherein the inhibitory receptor for tumor associated lipid antigens and superantigens are deleted or functionally deactivated.

10. The lipid-based tumor associated antigens of claims 1, 2, 4, 6, 9, wherein said lipid-based tumor associated antigen is selected from the group consisting of glycolipids, proteolipids, glycosphingolipids, sphingolipids, gangliosides, phytoglycolipids.

11. The lipid antigens derived from bacteria, mycobacteria, fungi and protozoa marine invertebrates of claim 2 wherein said lipid antigens are selected from the group consisting of glycosylceramides, glyco lipids, proteolipids, glyco sphingo lipids, gangliosides and sphingolipids with inositolphosphate-containing head groups, phytoglycolipids, mycoglycolipids, lipoarabinan and mycolic acid.

12 The sphingolipid antigens of claim 11 wherein the sphingolipid contains inositolphosphate-containing head groups with the general structure of ceramide-P-myoinositol-X with X referring to polar substituents consisting of ceramide-p-inositol-mannose, inositol-1-P-(6)mannose(a1,2inositol-1P-(1)ceramide, (inositol-P)2-ceramide, inositol-P-inositol-P-ceramide, inositol-P-inositol-P-ceramide.

13. The mammalian cell of claim 6-9 wherein said cell is an immunocyte selected from a group consisting of T cell, NK cell, NKT cells

14. A mammalian cell of claim 7 wherein the superantigen is selected from a group consisting of a staphylococcal enterotoxin, a streptococcal pyrogenic exotoxin, mycoplasma arthitides, rabies antigen, clostridial product.

15. A mammalian cell useful in the treatment of cancer wherein the inhibitory receptor for glycan-based tumor associated antigens is deleted or functionally deactivated.

16. The glycan antigens of claim 15 wherein said glycan antigen is selected from the group consisting of peptidoglycans or glycan phosphotidylinositol (GPI) structures.

17. A mammalian cell useful in the treatment of cancer wherein the the inhibitory receptor for superantigen-associated self antigens are functionally deleted or inactivated.

18. The self antigens of claims 17 wherein said self antigens consist of a MHC or CD1 molecule.

19. A mammalian cell useful in the treatment of cancer wherein the inhibitory receptors and/or immune receptor tyrosine based inhibitory motifs which inhibits cellular activation by receptors specific for lipid-based tumor associated antigens and superantigens are deleted or functionally deactivated.

20. The superantigen of claims 17 wherein said superantigen is selected from a group consisting of the staphylococcal enterotoxins SEA, SEB, SEC, SEC1, SEC2, SEC3, SED, SEE, TSST-1 or streptococcal pyrogenic exotoxins, mycoplasma arthritides, rabies virus, mammary tumor virus, clostridial antigen.

21. A mammalian cell in which the inhibitory receptor for lipid-based infectious disease associated antigens and/or immune receptor tyrosine

based inhibitory motifs which inhibits cellular activation by receptors specific for lipid-based infectious disease associated antigens derived from bacteria, fungi, mycobacteria, parasite, virus, eukaryote or prokaryote antigens are deleted or functionally deactivated.

22. The mammalian cell of claims 13, 14, 15, 17, 18, 21 wherein said cell is an immunocyte selected from a group consisting of T cells, NK cells, NKT cells

23. The lipid antigens of claims 21 wherein said lipid-based infectious disease associated antigen or fatty acid is mycolic acid or lipoarabinan,

24 A method of treating cancer in a mammal, said method comprising inactivating or deleting inhibitory receptors or immune receptor tyrosine based inhibitory motifs in immunocytes which inhibit activating receptors specific for lipid-based tumor associated lipid antigens or superantigens.

25. A method of inactivation or deletion of receptors or ITIMs in immunocytes which inhibit cell activating receptors specific for lipid-based tumor associated antigens and superantigens comprising inactivation or deletion of nucleic acids encoding ITIMs.

26. A method for producing a tumoricidal immunocyte population in vivo said method comprising allowing a tumor associated lipid antigen and superantigen to contact immunocyte activation receptors specific for tumor associated lipid antigens and superantigens in which inhibitory receptors or ITIMs which inhibit said cell activation by receptors specific for lipid-based tumor associated antigens are inactivated or deleted.

27. A method for producing a tumoricical immunocyte population ex vivo, said method comprising: a) allowing a lipid-based tumor associated antigen and superantigen to contact immunocyte activation receptors specific for lipid-based tumor associated antigens and superantigens in which inhibitory receptors or ITIMs which inhibit said cell activating receptors for lipid-based tumor associated antigens are deleted or inactivated. b) administering said tumoricidally activated immunocytes to the host.

28. A method of producing a immunocyte population effective against infectious disease in a mammal in vivo said method comprising: a) allowing a lipid-based infectious disaease associated antigen and superantigen to contact immunocyte activation receptors specific for and superantigens in which inhibitory receptors or ITIMs which inhibit said cell activation receptors specific for lipid-based infectious disaease associated antigen and superantigens are inactivated or deleted.

29. A method for producing an immunocyte population effective against infectious disease in a mammal ex vivo, said method comprising: a) allowing a lipid-based infectious disease associated antigen and superantigen to contact immunocyte activation receptors specific for lipid-based infectious disease associated antigens and superantigens in which inhibitory receptors or inhibitory receptors with tyrosine-based inhibitory motifs which inhibit said cell activating receptors for lipid-based infectious disease associated antigens are deleted or inactivated. b) administering said immunocyte population effective against infectious disease to the host.

30. The immunocytes of claims 26-29 wherein the said immunocytes comprise a group consisting of a T cell, NK cell or NKT cell

31. The immunocytes of claim 27, 29 wherein the said immunocytes are expanded in cytokines ex vivo prior to said administration

32. The method of claims 27-30 wherein said superantigen comprises a staphylococcal enterotoxin, a streptococcal pyrogenic exotoxin, mycoplasma arthritites, rabies virus, clostridial antigen, heat shock protein.

33. The staphylococcal enterotoxin of claim 32, wherein said enterotoxin is selected from the group consisting of SEA, SEB, SEC1, SEC2, SED, SEE, SEF, TSST-1, SPEA, SPEB, SPEC, Streptococcal pyogenic exotoxin.

34. The superantigen of any of the claims wherein said superantigen is expressed by a tumor cell or accessory cell which has been transfected with a nucleic acid encoding a superantigen.

35. The superantigen of claims 34 wherein said superantigen is expressed on the surface of a cell.

36. The cell of claim 35 wherein said cell is a tumor cell or an accessory cell.

37. The superantigen transfected tumor cell or accessory cell of claims 34-36 comprising transfecting said transfected cell with additional nucleic acids selected from a group comprising an adhesion molecule, an MHC molecule, a costimulatory molecule or a plurality thereof wherein said transfected cell expresses said encoded molecule(s) from said nucleic acid.

38. The transfected tumor cell or accessory cell of claims 34-37 wherein said transfected cell is transfected in vivo.

39. The transfected tumor cell or accessory cell of claims 34-37 wherein said transfected cell is transfected ex vivo.

40. A mammalian cell wherein inhibitory receptors or their ITIMs and Fas ligand receptors are deleted or functionally inactivated

41. The mammalian cell of claim 30, 31 wherein said cell is an immunocyte selected from a group consisting of T cell, NK cell, NKT cells

42. A method of treating cancer by wherein lipid-based tumor associated antigen or superantigen agonist motifs selectively contact immunocyte activating receptors and not immunocyte inhibitory receptors in vivo thereby producing an immunocyte population which is effective in the treatment of cancer.

43. A method of treating cancer by wherein lipid-based tumor associated antigen or superantigen agonist motifs selectively contact immunocyte activating receptors and not immunocyte inhibitory receptors ex vivo thereby producing an immunocyte population which is administered to the host and is effective in the treatment of cancer.

44. A method of treating infectious disease wherein lipid based infectious disease associated antigen agonist motifs selectively contact immunocyte activating receptors and not immunocyte inhibitory receptors in vivo thereby producing an immunocyte population effective in the treatment of infectious disease.

45. A method of treating infectious disease wherein lipid-based infectious disease associated antigens or superantigen agonist motifs selectively contact immunocyte activating receptors and not immunocyte inhibitory receptors ex vivo thereby producing an immunocyte population which is administered to the host and is effective in the treatment of infectious disease.

46. A method of treating infectious disease wherein lipid-based tumor associated antigens, lipid-based infectious disease associated antigens

of superantigen antagonist motifs are deleted or blocked from contact with immunocyte inhibitory receptors thereby allowing agonist motifs to stimulate immunocyte activating receptors to produce an immunocyte population which is effective in the treatment of cancer or infectious disease.

47. A method of treating cancer and infectious disease according to claims wherein the immunocytes are transfected with HSV thymidine kinase gene which induces immunocyte death in vivo in response to exogenous administration of gancyclivir.

48. An mammalian antigen presenting cell wherein MHC class I molecules molecules of said cell are deleted or inactivated rendering said cell capable of presenting tumor associated lipid antigens and superantigens to immunocytes which are then capable of inducing a tumoricidal response,

49. An mammalian antigen presenting cell wherein MHC class I molecules molecules of said cell are deleted or inactivated rendering said cell capable of presenting infectious disease associated lipid antigens and superantigens to immunocytes which induce an effective response against infectious disease.

50. A mammalian cell comprising a fusion of a tumor cell with a mammalian cell whereby said fusion cell expresses glycosylceramides and tumor antigens.

51. A mammalian cell comprising a fusion of a tumor cell with a mammalian or invertebrate cell whereby said fusion cell expresses tumor antigens and phytosphingolipids.

52. The fusion cells of claims 50, 51 wherein the said fusion cells are transfected with superantigen genes whereby said fusion cell expresses a superantigen.

53. A pharmacuetical composition useful in treatment of cancer comprising a lipid-based tumor associated antigen conjugated to a superantigen.

54. The composition of claim 53 wherein the lipid-based tumor associated antigen is selected from a group consisting of a glycolipid, proteolipid, glycosphingolipid, ganglioside.

55. A pharmaceutical preparation useful in the treatment of infectious disease comprising a lipid-based infectious disease associated antigen conjugated to a superantigen

56. The composition of claim 55 wherein the infectious disease associated lipid antigen is selected from a group consisting of a glycolipid, proteolipid, glycosphingolipid, ganglioside , phytosphingolipid, mycosphingolipid, lioarabinan or mycolic acid

57. The composition of claim 56 wherein the sphingolipid contains inositolphosphate-containing head groups with the general structure of ceramide-P-myoinositol-X with X referring to polar substituents consisting of ceramide-p-inositol-mannose, inositol-1-P-(6)mannose(a1,2inositol-1P-(1)ceramide, (inositol-P)2-ceramide, inositol-P-inositol-P-ceramide, inositol-P-inositol-P-ceramide.

58. A pharmacuetical composition useful in the treatment of cancer comprising a tumor associated glycan antigen conjugated to a superantigen.

59. The composition of claim 58 wherein the glycan is selected from a group consisting of a peptidoglycan or glycan-phosphotidyinositol (GPI) structures.

60. The compositions of claims 53-59 wherein the conjugates are bound to an MHC or CD1 receptor.

L12 ANSWER 13 OF 38 USPATFULL on STN

2003:200450 Autologous adoptive immunotherapy with antigen-specific primed T cells or B cells to promote antigen-specific immune responses with an appropriate cytokine bias.

Newell, Martha K., Colorado Springs, CO, UNITED STATES
Wade, William F., Lebanon, NH, UNITED STATES

US 2003138433 A1 20030724

APPLICATION: US 2002-225313 A1 20020821 (10)

PRIORITY: US 1999-139925P 19990617 (60)

DOCUMENT TYPE: Utility; APPLICATION.

AB The invention relates to methods and compositions for promoting antigen-specific immune responses with an appropriate cytokine bias. More specifically, the present invention relates to methods of using autologous adoptive immunotherapy with antigen-specific, ex vivo-primed T cells or B cells to promote antigen-specific immune responses with a **Th1** or **Th2** cytokine bias.

CLM What is claimed is:

1. A method of autologous adoptive immunotherapy, comprising: obtaining B cells that have been originally isolated from a subject and subsequently contacted in vitro with a target antigen conjugate to produce target antigen manipulated B cells, and infusing the target antigen manipulated B cells into the subject, wherein the target antigen conjugate comprises a target antigen that elicits a **Th2** response conjugated to an antibody that selectively binds a B cell cell-surface immunoglobulin.

2. The method of claim 1, wherein the target antigen manipulated B cells enhance an antigen-specific immune cell response to the target antigen that elicits a **Th2** response in a subject.

3. The method of claim 1, wherein the isolated B cells are mature B cells.

4. The method of claim 1, wherein the B cells are isolated from peripheral blood or an in vitro hematopoietic progenitor cell culture.

5. The method of claim 1, wherein the in vitro contacting of the isolated B cells with a target antigen conjugate, further comprises contacting the isolated B cells with an agent selected from the group consisting of a B cell co-stimulating agent and a **Th2** cytokine.

6. The method of claim 5, wherein the B cell co-stimulating agent is selected from the group consisting of TSA-1, CD2, CD5, CD24, CD28, CD40L, CD49a, CD80, CD81 and Cd86.

7. The method of claim 5, wherein the **Th2** cytokine is selected from the group consisting of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13.

8. A method of autologous adoptive immunotherapy, comprising: obtaining CD4+ helper T cells that have been originally isolated from a subject and subsequently contacted in vitro with a target antigen-conjugate to produce target antigen manipulated CD4+ helper T cells, and infusing the target antigen manipulated CD4+ helper T cells into the subject, wherein the target antigen conjugate comprises a target antigen that elicits a **Th2** response conjugated to an antibody that selectively binds a **T cell receptor**.

9. The method of claim 8, wherein the target antigen manipulated CD4+ helper T cells enhance an antigen-specific immune cell response to the target antigen that elicits a **Th2** response in a subject.

10. The method of claim 9, wherein the CD4+ helper T cells are isolated from peripheral blood or an in vitro hematopoietic progenitor cell culture.

11. The method of claim 8, wherein the in vitro contacting of isolated CD4+ helper T cells with a target antigen-conjugate, further comprises contacting the isolated CD4+ helper T cells with a **Th2** cytokine.

12. The method of claim 8, wherein the **Th2** cytokine is selected from the group consisting of IL-4, IL-5, IL-6, IL-9, IL-10, and 1L-13.

13. A method of autologous adoptive immunotherapy, comprising: obtaining CD4+ helper T cells that have been originally isolated from a subject and subsequently contacted in vitro with a target antigen-conjugate to produce target antigen manipulated CD4+ helper T cells, and infusing the target antigen manipulated CD4+ helper T cells into the subject, wherein the target antigen conjugate comprises a target antigen that elicits a **Th1** response, conjugated to a bi-specific antibody that selectively binds both a **T cell receptor** and CD4.

14. The method of claim 13, wherein the CD4+ helper T cells are isolated from peripheral blood or an in vitro hematopoietic progenitor cell culture.

15. The method of claim 13, wherein the in vitro contacting of the isolated CD4+ helper T cells with a target antigen-conjugate, further comprises contacting the isolated CD4+ helper T cells with a **Th1** cytokine.

16. The method of claim 15, wherein the **Th1** cytokine is selected from the group consisting of IL-2, TNF-α, IFN-γ, and lymphotoxin.

17. A target antigen-specific immune cell response enhancing composition, comprising: a target antigen conjugated to an antibody that selectively binds a B cell cell-surface immunoglobulin, wherein the target antigen elicits a **Th2** response.

18. A target antigen-specific immune cell response enhancing composition, comprising: a target antigen conjugated to an antibody that selectively binds a **T cell receptor**, wherein the target antigen elicits a **Th2** response.

19. A target antigen-specific immune cell response enhancing composition, comprising: a target antigen conjugated to a bi-specific antibody that selectively binds both a **T cell receptor** and CD4, wherein the target antigen elicits a **Th1** response.

20. A target antigen-specific immune cell response enhancing composition, comprising: an isolated B cell contacted in vitro with a target antigen conjugated to an antibody that selectively binds a B cell cell-surface immunoglobulin, wherein the target antigen elicits a **Th2** response, and a pharmaceutically acceptable carrier.

21. A target antigen-specific immune cell response enhancing composition, comprising: an isolated CD4+ helper T cell contacted in vitro with a target antigen conjugated to an antibody that selectively binds a **T cell receptor**, wherein the target antigen elicits a **Th2** response, and a pharmaceutically acceptable carrier.

22. A target antigen-specific immune cell response enhancing composition, comprising: an isolated CD4+ helper T cell contacted in vitro with a target antigen conjugated to a bi-specific antibody that selectively binds both a **T cell receptor** and CD4, wherein the target antigen elicits a **Th1** response, and a pharmaceutically

acceptable carrier.

L12 ANSWER 14 OF 38 USPATFULL on STN
2003:174213 **T cell receptor** Vbeta-Dbeta-Jbeta sequence and methods for its detection.
Zhang, Jingwu Z., Missouri City, TX, UNITED STATES
Baylor College of Medicine (U.S. corporation)
US 2003120061 A1 20030626
APPLICATION: US 2002-272339 A1 20021016 (10)
PRIORITY: US 1999-121311P 19990223 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In one embodiment, the present invention is directed to a first oligonucleotide comprising the sequence of or derived from 5'-CTAGGGCGGGCGGGACTCACCTAC-3'or the nucleic acid sequence complementary thereto. The first oligonucleotide can be used with a nucleic acid of between 15 and 30 nucleotides that does not comprise the sequence of the first oligonucleotide and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **V**β13.1 T cells, wherein the sequences of the oligonucleotide and the nucleic acid are not found on the same strand of the **V**β13.1 gene pair, to amplify a portion of the **V**β13.1 gene. Alternatively, the first oligonucleotide can be used with a labeling moiety in methods of detecting a LGRAGLTY motif found in T cell receptors of **V**β13.1 T cells. This motif is associated with autoimmune diseases, such as multiple sclerosis (MS). Once the motif is detected, the autoimmune disease can be treated or its progress monitored. The autoimmune disease can be treated by administering one or more **peptides** comprising the LGRAGLTY motif.

CLM What is claimed is:
1. An oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto.

2. The oligonucleotide of claim 1, which comprises at least 15 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto.

3. The oligonucleotide of claim 1, which comprises the sequence of SEQ ID NO: 1, or the nucleic acid complementary thereto.

4. A primer pair, comprising: (a) a first primer of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto; and (b) a second primer comprising a nucleic acid of about 15 and 30 nucleotides in length that does not comprise the sequence of (a) and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **T cell receptor** T cells, wherein the sequences of said first and second primers are not found on the same strand of the **T cell receptor** gene.

5. The primer pair of claim 4, wherein the **V**β13.1 gene sequence is SEQ ID NO: 2.

6. An oligonucleotide probe comprising: (a) an oligonucleotide of about 10 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto; and (b) a labeling moiety.

7. The oligonucleotide probe of claim 6, wherein the labeling moiety is selected from ^{32P} or digoxingenin.

8. A method of detecting MBP83-99 **V**β13.1 T cells expressing a **T cell receptor** LGRAGLTY motif, comprising: (a) obtaining a

nucleic acid sample from MBP83-99 vβ13.1 T cells; (b) contacting the nucleic acid sample with a primer pair selected or derived from: (i) a first oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto; and (ii) a second oligonucleotide of about 15 and 30 nucleotides in length that does not comprise the sequence of the first oligonucleotide and is found in the region from vβ to Jβ of the vβ13.1 gene in **T cell receptor** T cells, wherein the sequences of the first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene; and (c) detecting the presence of the nucleic acid encoding the LGRAGLTY motif.

9. The method of claim 8, wherein the vβ13.1 gene sequence is SEQ ID NO: 2.

10. The method according to claim 8, wherein a fragment of the nucleic acid sample is amplified by polymerase chain reaction (PCR).

11. The method according to claim 10, wherein the detection step comprises probing with an oligonucleotide probe comprising: i) an oligonucleotide, which comprises the sequence of SEQ ID NO: 1, or the nucleic acid complementary thereto; and, ii) a labeling moiety.

12. The method according to claim 10, wherein the detection step comprises autoradiography.

13. A test kit comprising a first oligonucleotide of about 15-30 nucleotides in length: said first oligonucleotide comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto.

14. The test kit of claim 13, further comprising: a second oligonucleotide of about 15 and 30 nucleotides in length that does not comprise the sequence of said first oligonucleotide and is found in the region from vβ to Jβ of the vβ13.1 gene in **T cell receptor** T cells, wherein the sequences of the first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene.

15. The test kit of claim 14, wherein the vβ13.1 gene sequence is SEQ ID NO: 2.

16. The test kit of claim 13, further comprising a labeling moiety, wherein the labeling moiety is selected from ^{32P} or digoxingenin.

17. A **peptide** of from 8 to approximately 45 amino acids in length, comprising the sequence of SEQ ID NO: 3.

18. The **peptide** of claim 17 which is SEQ ID NO: 3.

19. The **peptide** of claim 17 which comprises amino acids 2-21 of SEQ ID NO: 32.

20. The **peptide** of claim 17 which consists of amino acids 2-21 of SEQ ID NO: 32.

21. A method of treating an autoimmune disease, in a human comprising: (a) obtaining MBP83-99 vβ13.1 T cells from a human; (b) obtaining a nucleic acid sample from MBP83-99 vβ13.1 T cells; (c) contacting the nucleic acid sample with a primer pair selected or derived from: (i) a first oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto; and (iii) a second oligonucleotide of about 15 and 30 nucleotides in length that does not

comprise the sequence of said first oligonucleotide and is found in the region from **v**β to Jβ of the **v**β13.1 gene in **T cell receptor** T cells, wherein the sequences of said first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene; and (d) detecting the presence of the nucleic acid encoding the LGRAGLTY motif, and, if the nucleic acid is detected, (e) administering a **peptide** of from 8 to approximately 45 amino acids in length, **peptide** to the human; wherein the **peptide** comprising the sequence of SEQ ID NO: 3.

22. The method of 21, wherein the **v**β13.1 gene sequence is SEQ ID NO: 2.

23. The method of claim 21, wherein the administering step further comprises administering a T cell activation marker **peptide**.

24. The method of 21 wherein the **peptide** consists of the sequence of SEQ ID NO: 3.

25. The method of 21 wherein the **peptide** consists of amino acids 2-21 of SEQ ID NO: 32.

26. A method of monitoring an autoimmune disease, comprising: (A) obtaining MBP83-99 **v**β13.1 T cells from a human; (B) detecting the presence of a nucleic acid encoding a LGRAGLTY motif by (i) obtaining a nucleic acid sample from MBP83-99 **v**β13.1 T cells; (ii) contacting the nucleic acid sample with a primer pair selected or derived from: (a) a first oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO: 1, or the nucleic acid complementary thereto; and (b) a second oligonucleotide of about 15 and 30 nucleotides in length that does not comprise the sequence of said first oligonucleotide and is found in the region from **v**β to Jβ of the **v**β13.1 gene in **T cell receptor** T cells, wherein the sequences of said first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene; and (c) detecting the presence of the nucleic acid encoding the LGRAGLTY motif; and, if the nucleic acid is detected, (C) quantifying the amount of the nucleic acid.

27. The method of 26, wherein the **v**β13.1 gene sequence is SEQ ID NO: 2.

L12 ANSWER 15 OF 38 USPATFULL on STN
2003:119709 Compositions and methods for diagnosis and therapy of malignant mesothelioma.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Cheever, Martin A., Mercer Island, WA, UNITED STATES
US 2003082194 A1 20030501
APPLICATION: US 2001-791477 A1 20010222 (9)
PRIORITY: US 2000-184070P 20000222 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are compositions and methods for the diagnosis and therapy of Wilms' tumor antigen-associated cancers, and in particular, malignant pleural mesothelioma. In particular embodiments, the invention provides new, effective methods, compositions and kits for eliciting immune and T cell response to Wilms' tumor antigen **polypeptide**-derived antigenic fragments, and methods for the use of such compositions for diagnosis, detection, treatment, monitoring, and/or prevention of human malignant pleural mesothelioma

CLM What is claimed is:
1. A method of generating an immune or a T-cell response in an animal comprising administering to said animal a composition that comprises at least a first isolated **peptide** of from 9 to about 40 amino acids in

length, or at least a first nucleic acid segment that encodes said **peptide**, wherein said **peptide** comprises a first contiguous amino acid sequence according to any one of SEQ ID NO: 1 to SEQ ID NO:4, SEQ ID NO:13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326.

2. The method of claim 1, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 35 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

3. The method of claim 2, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 30 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

4. The method of claim 3, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 25 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

5. The method of claim 4, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 20 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

6. The method of claim 5, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 15 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

7. The method of claim 6, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 13 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

8. The method of claim 7, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 11 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**.

9. The method of claim 9, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said **peptide** comprising a first contiguous amino acid sequence according to any one of SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326.

10. The method of claim 9, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said **peptide** comprising a first contiguous amino acid sequence according to any one of SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318.

11. The method of claim 10, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said **peptide** comprising at least a first contiguous amino acid sequence selected from the group consisting of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO:199, and SEQ ID NO:282.

12. The method of claim 11, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 11 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said **peptide** consisting essentially of the amino acid sequence of any one of SEQ ID NO:1 to SEQ ID NO:4, SEQ ID NO: 13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326.

13. The method of claim 12, wherein said composition comprises at least

a first isolated **peptide** of from 9 to about 11 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said **peptide** consisting essentially of the amino acid sequence of any one of SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:316 to SEQ ID NO:318.

14. The method of claim 13, wherein said composition comprises at least a first isolated **peptide** of from 9 to about 11 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said **peptide** consisting essentially of the amino acid sequence of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO: 199, or SEQ ID NO:282.

15. The method of claim 14, wherein said composition comprises at least a first isolated **peptide** that consists of the amino acid sequence according to any one of SEQ ID NO:1 to SEQ ID NO:4, SEQ ID NO:13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326, or at least a first nucleic acid segment that encodes said **peptide**.

16. The method of claim 15, wherein said composition comprises at least a first isolated **peptide** that consists of the amino acid sequence according to any one of SEQ ID NO: 13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:316 to SEQ ID NO:318, or at least a first nucleic acid segment that encodes said **peptide**.

17. The method of claim 16, wherein said composition comprises at least a first isolated **peptide** that consists of the amino acid sequence of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO:199, or SEQ ID NO:282; or at least a first nucleic acid segment that encodes said **peptide**.

18. The method of claim 1, wherein said composition further comprises at least a second isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said second **peptide** comprising at least a first contiguous amino acid sequence according to any one of SEQ ID NO:1 to SEQ ID NO:4, SEQ ID NO:13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326.

19. The method of claim 18, wherein said composition further comprises at least a second isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said second **peptide** comprising at least a first contiguous amino acid sequence according to any one of SEQ ID NO: 13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:316 to SEQ ID NO:318.

20. The method of claim 19, wherein said composition further comprises at least a second isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said second **peptide** comprising at least a first contiguous amino acid selected from the group consisting of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO: 185, SEQ ID NO: 198, SEQ ID NO: 199, and SEQ ID NO:282.

21. The method of claim 1, wherein said composition further comprises at least a third isolated **peptide** of from 9 to about 40 amino acids in length, or at least a first nucleic acid segment that encodes said **peptide**; said third **peptide** comprising at least a first contiguous amino acid sequence according to any one of SEQ ID NO:1 to SEQ ID NO:4, SEQ ID NO: 13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID

to SEQ ID NO:326.

22. The method of claim 21, wherein said third **peptide** comprises at least a first contiguous amino acid sequence according to any one of SEQ ID NO: 13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:316 to SEQ ID NO:318.

23. The method of claim 22, wherein said third **peptide** comprises at least a first contiguous amino acid selected from the group consisting of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO:199, and SEQ ID NO:282.

24. The method of claim 1, wherein said composition comprises at least a first nucleic acid segment of from 27 to about 5000 nucleotides in length.

25. The method of claim 24, wherein said composition comprises at least a first nucleic acid segment of from 27 to about 3000 nucleotides in length.

26. The method of claim 25, wherein said composition comprises at least a first nucleic acid segment of from 27 to about 1000 nucleotides in length.

27. The method of claim 26, wherein said composition comprises at least a first nucleic acid segment of from 27 to about 500 nucleotides in length.

28. The method of claim 1, wherein said first nucleic acid segment is operably positioned under the control of at least a first heterologous promoter.

29. The method of claim 1, wherein said first nucleic acid segment is comprised within a vector.

30. The method of claim 29, wherein said first nucleic acid segment is comprised within a plasmid or viral vector.

31. The method of claim 1, wherein said composition further comprises a pharmaceutically acceptable excipient.

32. The method of claim 1, wherein said composition further comprises at least a first immunostimulant or at least a first adjuvant.

33. The method of claim 32, wherein said at least a first immunostimulant or said at least a first adjuvant preferentially enhances a T-cell response in a human.

34. The method of claim 32, wherein said at least a first immuno stimulant or said at least a first adjuvant is selected from the group consisting of Montanide ISA50, Seppic Montanide ISA720, a cytokine, a microsphere, a dimethyl dioctadecyl ammonium bromide adjuvant, AS-1, AS-2, Ribi Adjuvant, QS21, saponin, microfluidized Syntex adjuvant, MV, ddMV, an immune stimulating complex and an inactivated toxin.

35. The method of claim 1, wherein said animal is a human

36. The method of claim 35, wherein said human is a patient

37. The method of claim 1, wherein said composition is administered to a patient that has, is suspected of having, or is at risk for developing mesothelioma.

38. The method of claim 36, wherein said composition is administered to

a patient that has, is suspected of having, or is at risk for developing malignant pleural mesothelioma.

39. The method of claim 1, wherein said composition is formulated for parenteral, intravenous, intraperitoneal, subcutaneous, intranasal, transdermal, or oral administration to said animal.

40. The method of claim 1, wherein said composition further comprises at least a first detection reagent.

41. The method of claim 40, wherein said detection reagent comprises a radiolabel, a spin label, or a fluorogenic, chromogenic, or a chemiluminescent label.

42. The method of claim 40, wherein said detection reagent specifically binds to a WT1 **peptide**, **polypeptide**, or antibody or antigen binding fragment specific therefor.

43. The method of claim 1, wherein said composition further comprises at least a second therapeutic agent for treating or preventing mesothelioma.

44. The method of claim 1, wherein said second therapeutic agent further comprises at least a second immunostimulant or at least a second adjuvant.

45. A method of inhibiting the biological activity of a WT1 **polypeptide** in a patient having, suspected of having, or at risk for developing malignant mesothelioma, comprising administering to said patient an effective amount of at least a first composition that comprises: (a) at least a first isolated **peptide** of from 9 to about 40 amino acids in length; (b) at least a first nucleic acid segment that encodes said **peptide**; (c) at least a first antibody or at least a first antigen binding fragment thereof having immunospecificity for said **peptide**; or (d) at least a first antigen-presenting cell or at least a first T cell that specifically binds to said **peptide**; wherein said **peptide** comprises a first contiguous amino acid sequence according to any one of SEQ ID NO:1 to SEQ ID NO:4, SEQ ID NO:13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326.

46. The method of claim 45, wherein inhibiting the biological activity of said WT1, **polypeptide** in said patient comprises administering to said patient an effective amount of at least a first composition that comprises: (a) at least a first isolated **peptide** of from 9 to about 40 amino acids in length, or (b) at least a first nucleic acid segment that encodes said **peptide**.

47. The method of claim 46, wherein inhibiting the biological activity of said WT1 **polypeptide** in said patient comprises administering to said patient an effective amount of at least a first composition that comprises: (a) at least a first isolated **peptide** of from 9 to about 40 amino acids in length, or (b) at least a first nucleic acid segment that encodes said **peptide**, and further wherein said **peptide** comprises at least a first contiguous amino acid sequence according to any one of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO:199, and SEQ ID NO:282.

48. The method of claim 46, wherein inhibiting the biological activity of said WT1 **polypeptide** in said patient comprises administering to said patient an effective amount of at least a first composition that comprises: (a) at least a first antibody or at least a first antigen binding fragment thereof having immunospecificity for said **peptide**; or (b) at least a first antigen-presenting cell or at least a first T cell that specifically binds to said **peptide**, and further wherein said

peptide comprises at least a first contiguous amino acid sequence according to any one of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO: 147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO:199, and SEQ ID NO:282.

49. A method of treating or preventing malignant mesothelioma in a patient having, suspected of having, or at risk for developing said mesothelioma, said method comprising administering to said patient a therapeutically-effective amount of at least a first composition that comprises: (a) at least a first isolated **peptide** of from 9 to about 40 amino acids in length; (b) at least a first nucleic acid segment that encodes said **peptide**; (c) at least a first antibody or at least a first antigen binding fragment thereof having immunospecificity for said **peptide**; or (d) at least a first antigen-presenting cell or at least a first T cell that specifically binds to said **peptide**; wherein said **peptide** comprises a first contiguous amino acid sequence according to any one of SEQ ID NO: 1 to SEQ ID NO:4, SEQ ID NO: 13 to SEQ ID NO:20, SEQ ID NO:28 to SEQ ID NO:311, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:316 to SEQ ID NO:318, and SEQ ID NO:321 to SEQ ID NO:326, for a time sufficient to treat or prevent said malignant mesothelioma.

50. The method of claim 49, wherein treating said malignant mesothelioma in a patient having or suspected of having said mesothelioma, comprises administering to said patient a therapeutically-effective amount of at least a first composition that comprises: (a) at least a first isolated **peptide** of from 9 to about 40 amino acids in length; (b) at least a first nucleic acid segment that encodes said **peptide**; (c) at least a first antibody or at least a first antigen binding fragment thereof having immunospecificity for said **peptide**; or (d) at least a first antigen-presenting cell or at least a first T cell that specifically binds to said **peptide**; wherein said **peptide** comprises a first contiguous amino acid sequence according to any one of SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:49, SEQ ID NO:88, SEQ ID NO:144, SEQ ID NO:147, SEQ ID NO:185, SEQ ID NO:198, SEQ ID NO:199, and SEQ ID NO:282, for a time sufficient to treat said malignant mesothelioma.

L12 ANSWER 16 OF 38 USPATFULL on STN
2003:113655 Compositions and methods for the detection, diagnosis and therapy of hematological malignancies.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Algate, Paul A., Issaquah, WA, UNITED STATES
Mannion, Jane, Edmonds, WA, UNITED STATES
Retter, Marc, Carnation, WA, UNITED STATES
Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)
US 2003078396 A1 20030424
APPLICATION: US 2001-40862 A1 20011106 (10)
PRIORITY: US 2000-223378P 20000807 (60)
US 2000-223416P 20000804 (60)
US 2000-222903P 20000803 (60)
US 2000-218950P 20000714 (60)
US 2000-206201P 20000522 (60)
US 2000-202084P 20000504 (60)
US 2000-202084P 20000504 (60)
US 2000-200999P 20000501 (60)
US 2000-200303P 20000428 (60)
US 2000-200779P 20000428 (60)
US 2000-200545P 20000427 (60)
US 2000-190479P 20000317 (60)
US 2000-186126P 20000301 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are methods and compositions for the detection, diagnosis, prognosis, and therapy of hematological malignancies, and in particular, B cell leukemias, lymphomas and multiple myelomas. Disclosed are compositions, methods and kits for eliciting immune and T cell responses

to specific malignancy related antigenic **polypeptides** and antigenic **polypeptide** fragments thereof in an animal. Also disclosed are compositions and methods for use in the identification of cells and biological samples containing one or more hematological malignancy-related compositions, and methods for the detection and diagnosis of such diseases and affected cell types. Also disclosed are diagnostic and therapeutic kits, as well as methods for the diagnosis, therapy and/or prevention of a variety of leukemias and lymphomas.

CLM What is claimed is:

1. An isolated polynucleotide encoding a protein less than about 300 amino acids comprising a sequence selected from the group consisting of: (a) sequence provided in SEQ ID NO:3; (b) complements of the sequence provided in SEQ ID NO:3; (c) sequences having at least 90% identity to a sequence of SEQ ID NO: 3; and (d) degenerate variants of a sequence provided in SEQ ID NO:3.

2. An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of: (a) sequences encoded by a polynucleotide of claim 1; and (b) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1; and (c) sequences provided in SEQ ID NOs:16-20; and (d) sequences provided in SEQ ID NOs:21-840; and (e) sequences provided in SEQ ID NOs:841-861.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a **polypeptide** of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of: (a) obtaining a biological sample from the patient; (b) contacting the biological sample with a binding agent that binds to a **polypeptide** of claim 2; (c) detecting in the sample an amount of **polypeptide** that binds to the binding agent; and (d) comparing the amount of **polypeptide** to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one **polypeptide** according to claim 2.

8. An oligonucleotide that hybridizes to nucleotides 1-630 of the sequence recited in SEQ ID NO:3 under moderately stringent conditions.

9. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of: (a) **polypeptides** according to claim 2; (b) polynucleotides according to claim 1; and (c) antigen-presenting cells that express a **polypeptide** according to claim 1, under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

10. An isolated T cell population, comprising T cells prepared according to the method of claim 9.

11. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of: (a) **polypeptides** according to claim 2; (b) polynucleotides according to claim 1; (c) antibodies according to claim 5; (d) fusion proteins according to claim 7; (e) T cell populations according to claim 10; and antigen presenting cells that express a **polypeptide** according to claim 2.

12. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 11.

13. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 11.

14. A method for determining the presence of a cancer in a patient, comprising the steps of: (a) obtaining a biological sample from the patient; (b) contacting the biological sample with an oligonucleotide according to claim 8; (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and (d) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

15. A diagnostic kit comprising at least one oligonucleotide according to claim 8.

16. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

17. A method for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) **polypeptides** according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a **polypeptide** of claim 2, such that T cell proliferate; (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

18. An isolated polynucleotide encoding a protein of less than 300 amino acids comprising a sequence selected from the group consisting of: (a) sequence provided in SEQ ID NO:6; (b) complements of the sequences provided in SEQ ID NO:6; (c) sequences having at least 90% identity to a sequence of SEQ ID NO: 6; and (d) degenerate variants of a sequence provided in SEQ ID NO:6.

19. An isolated **polypeptide** comprising an amino acid sequence selected from the group consisting of: (a) sequences encoded by a polynucleotide of claim 18; and (b) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 18; and (c) the sequence provided in SEQ ID NO:869.

20. An expression vector comprising a polynucleotide of claim 18 operably linked to an expression control sequence.

21. A host cell transformed or transfected with an expression vector according to claim 20.

22. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a **polypeptide** of claim 19.

23. A method for detecting the presence of a cancer in a patient, comprising the steps of: (a) obtaining a biological sample from the patient; (b) contacting the biological sample with a binding agent that binds to a **polypeptide** of claim 19; (c) detecting in the sample an amount of **polypeptide** that binds to the binding agent; and (d) comparing the amount of **polypeptide** to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

24. A fusion protein comprising at least one **polypeptide** according to claim 19.

25. A method for stimulating and/or expanding T cells specific for a

cancer process, comprising contacting a cell with at least one component selected from the group consisting of: (a) **polypeptides** according to claim 19; (b) polynucleotides according to claim 18; and (c) antigen-presenting cells that express a **polypeptide** encoded by a polynucleotide according to claim 18, under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

26. An isolated T cell population, comprising T cells prepared according to the method of claim 26.

27. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of: (a) **polypeptides** according to claim 19; (b) polynucleotides according to claim 18; (c) antibodies according to claim 22; (d) fusion proteins according to claim 24; (e) T cell populations according to claim 27; and antigen presenting cells that express a **polypeptide** according to claim 19.

28. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 28.

29. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 28.

30. A diagnostic kit comprising at least one oligonucleotide according to claim 25.

31. A diagnostic kit comprising at least one antibody according to claim 22 and a detection reagent, wherein the detection reagent comprises a reporter group.

32. A method for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) **polypeptides** according to claim 19; (ii) polynucleotides according to claim 18; and (iii) antigen presenting cells that express a **polypeptide** of claim 19, such that T cell proliferate; (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

L12 ANSWER 17 OF 38 USPATFULL on STN
2003:99216 Methods of administering/dosing CD2 antagonists for the prevention and treatment of autoimmune disorders or inflammatory disorders.
Dingivan, Christine, Germantown, MD, UNITED STATES
US 2003068320 A1 20030410
APPLICATION: US 2002-91268 A1 20020304 (10)
PRIORITY: US 2001-273098P 20010302 (60)
US 2001-346918P 20011019 (60)
US 2002-358424P 20020219 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions for the prevention or treatment of an autoimmune disorder or an inflammatory disorder in a subject comprising one or more CD2 antagonists. In particular, the invention provides methods for preventing or treating an autoimmune disorder or an inflammatory disorder in a subject comprising administering one or more CD2 binding molecules to said subject. The present invention provides doses of CD2 binding molecules and methods of administration that result in improved efficacy, while avoiding or reducing the adverse or unwanted side effects associated with the administration of an agent that induces the depletion of peripheral blood lymphocytes.
CLM What is claimed is:

1. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a dose of a therapeutically effective amount of one or more CD2 binding molecules, wherein administration of said dose results in CD2 binding molecules binding to at least 25% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes.

2. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a dose of a therapeutically effective amount of one or more CD2 binding molecules, wherein administration of said dose results in a mean absolute lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl.

3. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a dose of a therapeutically effective amount of one or more CD2 binding molecules, wherein administration of said dose results in an approximately 25% or more reduction in said subject's mean absolute lymphocyte count relative to said subject's mean absolute lymphocyte count prior to the administration of said dose.

4. The method of claim 2 further comprising administering to said subject one or more subsequent doses of a therapeutically effective amount of one or more CD2 binding molecules after administration of said first dose, wherein administration of said subsequent doses maintain a mean absolute lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl.

5. The method of claim 2 further comprising administering to said subject one or more subsequent doses of a therapeutically effective amount of one or more CD2 binding molecules after administration of said first dose, wherein administration of said subsequent doses maintain an approximately 25% or more reduction in said subject's absolute mean lymphocyte count relative to said subject's mean absolute lymphocyte count prior to the administration of said first dose.

6. The method of claim 4, wherein said subsequent dose is administered at least 1 week after the administration of said first dose.

7. The method of claim 1 further comprising administering to said subject one or more subsequent doses of a therapeutically effective amount of one or more CD2 binding molecules after administration of said first dose, wherein said administration of said subsequent doses restore at least 25% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes being bound by CD2 binding molecules.

8. The method of claim 1 or 3, wherein said dose results in CD2 binding molecules binding to at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75% or at least 80% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes for at least 1 hour after the administration of said dose and prior to the administration of a subsequent dose.

9. The method of claim 7, wherein said first dose results in CD2 binding molecules binding to at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75% or at least 80% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes.

10. The method of claim 7, wherein said first dose results in a mean

absolute lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl and said subsequent doses restore a mean absolute lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl.

11. The method of claim 3 or 9, wherein a subsequent dose is administered when the percentage of CD2 **polypeptides** bound to CD2 binding molecules drops to 20% or less, 15% or less, or 10% or less.

12. The method of claim 3 or 9, wherein a subsequent dose is administered when the mean absolute lymphocyte count increases to approximately 1250 cells/μl or more.

13. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof said method comprising administering to a subject in need thereof a dose of a therapeutically effective amount of one or more CD2 binding molecules and administering to said subject one or more subsequent doses of a therapeutically effective amount of one or more CD2 binding molecules after administering a prior dose, wherein said CD2 binding molecules do not inhibit the interaction between LFA-3 and CD2.

14. The method of claim 1, 2 or 3, wherein said CD2 binding molecules are not small organic molecules.

15. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising: (a) administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules; (b) monitoring the mean absolute lymphocyte count in said subject after the administration of one or more of said doses and prior to the administration of a subsequent dose; and (c) maintaining a mean absolute lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl by repeating step (a) as necessary.

16. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising: (a) administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules; (b) monitoring the mean absolute lymphocyte count of said subject after the administration of one or more of said doses and prior to the administration of a subsequent dose; and (c) maintaining a mean absolute lymphocyte count in said subject of 25% less than the mean absolute lymphocyte count in said subject prior to the administration of said doses of therapeutically effective amounts of one or more CD2 binding molecules by repeating step (a) as necessary.

17. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising: (a) administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules; and (b) monitoring the mean absolute lymphocyte count in said subject after administration of a certain number of doses and prior to the administration of a subsequent dose.

18. The method of claim 17, wherein the certain number of doses is 1, 2, 3, 4, 5, 6,7,8,9, 10, 11 or 12 doses.

19. The method of claim 18 further comprising administering one or more subsequent doses of a therapeutically effective amount of one or more CD2 binding molecules based upon whether the lymphocyte count is within the range of approximately 500 cells/μl to 1200 cells/μl.

20. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising: (a) administering to a subject in need thereof one or more

doses of a therapeutically effective amount of one or more CD2 binding molecules; (b) assessing the percentage of CD2 **polypeptides** bound by CD2 binding molecules after administration of one or more of said doses and prior to the administration of a subsequent dose; and (c) administering to said subject one or more subsequent doses of a therapeutically effective amount of one or more CD2 binding molecules when the percentage of CD2 **polypeptides** expressed by peripheral blood lymphocytes bound by CD2 binding molecules is approximately 20% or less.

21. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising: (a) administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules; (b) monitoring the percentage of CD2 **polypeptides** bound by CD2 binding molecules after administration of one or more of said doses and prior to the administration of a subsequent dose; and (c) maintaining at least a 25% receptor occupancy by said CD2 binding molecules in said subject by repeating step (a) as necessary.

22. A method of treating or ameliorating an autoimmune disorder or an inflammatory disorder or one or more symptoms thereof, said method comprising: (a) administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules; and (b) monitoring the percentage of CD2 **polypeptides** expressed by peripheral blood lymphocytes bound by CD2 binding molecules in said subject after administration of a certain number of doses and prior to the administration of a subsequent dose.

23. The method of claim 22, wherein the certain number of doses is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 doses.

24. A method of treating or ameliorating psoriasis or one or more symptoms thereof, said method comprising administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules, wherein administration of said doses results in a mean absolute lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl.

25. A method of treating or ameliorating psoriasis or one or more symptoms thereof, said method comprising administering to a subject in need thereof one or more doses of a therapeutically effective amount of one or more CD2 binding molecules, wherein administration of said doses results in at least 25% of CD2 **polypeptides** expressed by peripheral blood lymphocytes being bound by CD2 binding molecules.

26. The method of claim 25, wherein said doses result in CD2 binding molecules binding to at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75% or at least 80% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes.

27. A method of treating or ameliorating psoriasis or one or more symptoms thereof, said method comprising administering to a subject in need thereof one or more doses of a therapeutically effective amount of MEDI-507.

28. The method of claim 27, wherein administration of said doses results in a lymphocyte count of approximately 500 cells/μl to below 1200 cells/μl.

29. The method of claim 27, wherein administration of said doses results in at least 30% of CD2 **polypeptides** expressed by peripheral blood lymphocytes being bound by MEDI-507.

30. The method of claim 29, wherein said doses result in at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at

polypeptides expressed by peripheral blood lymphocytes being bound by MEDI-507.

31. The method of claim 24, 25, 26, 27 or 28, wherein at least a 25% reduction of said subject's Psoriasis Area and Severity Index (PASI) score is achieved.

32. The method of claim 31, wherein the PASI score is reduced by at least 50%.

33. The method of claim 31, wherein the PASI score is reduced by at least 75%.

34. A method of treating or ameliorating psoriasis in a human which method reduces or avoids adverse effects associated with decreasing lymphocyte counts, said method comprising administering doses of a therapeutically effective amount of one or more CD2 binding molecules, said doses being effective to achieve a reduction in said human's PASI score by at least 25% but insufficient to cause a reduction in lymphocyte count to below 500 cells/μl.

35. The method of claim 34, wherein at least a 50% reduction in said human's PASI score is achieved.

36. The method of claim 34, wherein the lymphocyte count is between 500 cells/μl and 1200 cells/μl.

37. The method as in any one of claims 1-5, 13, 17 and 22, wherein the autoimmune disorder is rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's Syndrome, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, multiple sclerosis, or myasthenia gravis.

38. The method as in any one of claims 1-5, 13, 17 and 22, wherein the inflammatory disorder is asthma, encephilitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), arthritis, or an allergic disorder.

39. The method as in any one of claims 1-5, 13, 17 and 22, wherein the autoimmune disorder is characterized by increased infiltration of lymphocytes into affected dermal or epidermal tissues.

40. The method as in any one of claims 1-5, 13, 17 and 22, wherein the autoimmune disorder is characterized by increased T cell activation or abnormal antigen presentation.

41. The method as in any one of claims 1-5, 13, 17 and 22, wherein the autoimmune disorder is psoriasis.

42. The method of claim 41, wherein the psoriasis is chronic plaque psoriasis.

43. The method of claim 1, 2, 3 or 13, wherein said dose is administered parenterally.

44. The method of claim 27, 28 or 29, wherein said doses of MEDI-507 are administered parenterally.

45. The method as in any one of claims 1-5, 13, 17, 22, and 24, wherein at least one of the CD2 binding molecules is a fusion protein.

46. The method as in any one of claims 1-5, 13, 17, 22, and 24, wherein at least one of the CD2 binding molecules is an antibody.

47. The method of claim 46, wherein the antibody is LO-CD2a/BTI-322 or

an antigen-binding fragment thereof.

48. The method of claim 46, wherein the antibody is a human or humanized monoclonal antibody.

49. The method of claim 46, wherein the antibody is MEDI-507 or an antigen-binding fragment thereof.

50. The method as in any one of claims 1-5, 13, 17, 22, 24, and 27-29, wherein said effective amount is a dose of approximately 150 μg/kg or less, approximately 125 μg/kg or less, approximately 100 μg/kg or less, approximately 75 μg/kg or less, approximately 50 μg/kg or less, approximately 40 μg/kg or less, approximately 30 μg/kg or less, approximately 20 μg/kg or less, approximately 10 μg/kg or less, approximately 5 μg/kg or less, approximately 2 μg/kg or less, approximately 1 μg/kg or less, or approximately 0.5 μg/kg or less.

51. The method as in any one of claims 1-5, 13, 17, 22, 24, and 27-29, wherein said effective amount is a dose of between approximately 0.05 μg/kg and 150 μg/kg.

52. The method as in any one of claims 1-5, 13, 17, 22, 24, and 27-29, wherein the subject is a human subject.

53. The method of claim 4, 5, or 7, wherein the first dose is administered parenterally.

54. The method of claim 4, 5, or 7, wherein the subsequent doses are administered parenterally.

55. The method of claim 1, 2, 3 or 13, wherein said dose is administered subcutaneously.

56. The method of claim 27, 28 or 29, wherein said doses of MEDI-507 are administered subcutaneously.

57. The method of claim 4, 5, or 7, wherein the first dose is administered subcutaneously.

58. The method of claim 4, 5, or 7, wherein the subsequent doses are administered subcutaneously.

59. An article of manufacture comprising packaging material and a pharmaceutical agent contained within said packaging material, wherein said pharmaceutical agent comprises a CD2 binding molecule and a pharmaceutically acceptable carrier, wherein said article of manufacture includes instruction means indicating a dosing regimen comprising administering an initial dosing, and optionally administering a subsequent dose or doses, of said pharmaceutical agent to a subject suffering from one or more symptoms associated with an autoimmune disorder or an inflammatory disorder, wherein the instruction means suggests a dosing regimen comprising an initial dosing that results in CD2 binding molecules binding to at least 30% of the CD2 **polypeptides** expressed by the subject's peripheral blood lymphocytes for at least 1 hour after the administration of said initial dosing, and wherein the instruction means suggests a dosing interval for said dosing regimen such that any dose/doses administered subsequent to said initial dosing, if administered, is/are only administered when 20% or less of the CD2 **polypeptides** expressed by peripheral blood lymphocytes are bound by previously administered CD2 binding molecules.

60. An article of manufacture comprising packaging material and a pharmaceutical composition in suitable form for administration to a human contained within said packaging material, wherein said

pharmaceutical composition comprises MAbI 3G7 or an antigen binding fragment thereof, and a pharmaceutically acceptable carrier.

L12 ANSWER 18 OF 38 USPATFULL on STN
2003:93021 Anergy-regulated molecules.
Rao, Anjana, Cambridge, MA, UNITED STATES
Byrne, Michael, Brookline, MA, UNITED STATES
Macian, Fernando, Quincy, MA, UNITED STATES
The Center For Blood Research, Inc., Boston, MA (U.S. corporation)
US 2003064380 A1 20030403
APPLICATION: US 2002-58024 A1 20020129 (10)
PRIORITY: US 2001-264876P 20010129 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the identification of novel targets for diagnosis, prognosis, therapeutic intervention and prevention of an immune disorder. In particular, the present invention is directed to the identification of novel targets which are anergy markers. The present invention is further directed to methods of high-throughput screening for test compounds capable of modulating the activity of proteins encoded by the novel targets. Moreover, the present invention is also directed to methods that can be used to assess the efficacy of test compounds and therapies for the ability to inhibit an immune disorder. Methods for determining the long term prognosis in a subject are also provided.

CLM What is claimed is:

1. A method of screening for test compounds capable of modulating the activity of an anergy marker protein encoded by an anergy marker listed in Group I or Group II or Group III or Group IV, the method comprising: a) contacting the anergy marker protein with a plurality of test compounds; b) detecting binding of one of the test compounds to the anergy marker protein, relative to other test compounds; and c) correlating the amount of binding of the test compound to the anergy marker protein with the ability of the test compound to modulate the activity of the anergy marker protein, wherein binding indicates that the test compound is capable of modulating the activity of the anergy marker protein and wherein the nucleic acid sequence of the anergy marker is 75% homologous to the anergy marker listed in Group I or Group II or Group III or Group IV.

2. The method of claim 1, wherein the method of screening is high-throughput screening.

3. The method of claim 1, wherein the test compound is from a library selected from a group of libraries consisting of spatially addressable parallel solid phase or solution phase libraries or synthetic libraries made from deconvolution, `one-bead one-compound` methods and by affinity chromatography selection.

4. The method of claim 1, wherein the selected test compound prevents binding of the anergy marker protein with a bioactive agent selected from the group consisting of naturally-occurring compounds, biomolecules, proteins, **peptides**, oligopeptides, polysaccharides, nucleotides and polynucleotides.

5. The method of claim 1, wherein the test compound is a bioactive agent selected from the group consisting of naturally-occurring compounds, biomolecules, proteins, **peptides**, oligopeptides, polysaccharides, nucleotides and polynucleotides.

6. The method of claim 1, wherein the test compound is a small molecule.

7. The method of claim 1, wherein the anergy marker is selected from the group consisting of Msa.21745.0_s_at (also Mm. 21985), Hs. 129764, U44731_s_at (also Mm. 1909), Hs. 240849, Msa.1669.0_f_at (also Mm.

19123), and GenBank PID:g2853176.

8. The method of claim 1, wherein the anergy marker is selected from the group consisting of Mm. 116802, Hs. 248037, Mm. 10085 and Hs. 96149.

9. The method of claim 1, wherein the anergy marker is selected from the group ET63436_at, k00083_s_at, MIP1-B_at, Msa.11439.0_s_at, Msa.15983.0_f_at, Msa.1669.0_f_at Msa.18713.0_g_at, U44731_s_at, x12531 s_at and x67914_s_at.

10. The method of claim 1, wherein the anergy marker is selected from the group consisting of GRG4, jumonji, RPTPσ, PTP-1B, RPTPκ, GBP-3, Rab10, SOCS-2, Traf5, DAGKα, LDHAα, phosphoglycerate mutase, CD98, 4-IBB-L, and FasL.

11. The method of claim 1, wherein the anergy marker is GBP-3.

12. A method of screening for test compounds capable of modulating the level of expression of an anergy marker, the method comprising the steps of comparing: a) a level of expression of an anergy marker listed in Group I or Group II or Group III or Group IV in a first sample of cells prior to providing a test compound to the first sample of cells; and b) a level of expression of the same anergy marker in a second sample of cells after providing the test compound to the second sample of cells, wherein a substantially modulated level of expression of the anergy marker in the second sample, relative to the first sample, is an indication that the test compound is capable of modulating the level of expression.

13. The method of claim 12, wherein the test compound is from a library selected from a group of libraries consisting of spatially addressable parallel solid phase or solution phase libraries or synthetic libraries made from deconvolution, `one-bead one-compound` methods and by affinity chromatography selection.

14. The method of claim 12, wherein the cell is an immune cell.

15. The method of claim 12, further comprising the step of stimulating the cells prior to providing the test compound.

16. The method of claim 15, wherein the step of stimulating the cells includes contacting the cells with a stimulant selected from the group consisting of an antigen, an antigen presenting cell, an activator of NFAT-NFAT ligand signaling, a combination of anti-CD3 and anti-CD28 antibodies, and a combination of anti-**TCR** and anti-CD28 antibodies.

17. The method of claim 16, wherein the activator of NFAT-NFAT ligand signaling is selected from the group consisting of ionomycin and PMA.

18. The method of claim 12, wherein the anergy marker is selected from the group consisting of Msa.21745.0_s_at (also Mm. 21985), Hs. 129764, U44731_s_at (also Mm. 1909), Hs. 240849, Msa.1669.0_f_at (also Mm. 19123), and GenBank PID:g2853176.

19. The method of claim 12, wherein the anergy marker is selected from the group consisting of Mm. 116802, Hs. 248037, Mm. 10085 and Hs. 96149.

20. The method of claim 12, wherein the anergy marker is selected from the group consisting of Z31202_s_at, aa144045_s_at, aa174748_at, c81206_rc_at, D86609_s_at, ET63436_at, k00083_s_at, MIP1-B_at, Msa.11439.0_s_at, Msa.15983.0_f_at, Msa.1669.0_f_at, Msa.18713.0_g_at, U44731_s_at, x12531_s_at, and x67914_s_at.

21. The method of claim 12, wherein the anergy marker is selected from the group consisting of GRG4, jumonji, RPTPσ, PTP-1B, RPTPκ, GBP-3, Rab10, caspase-3, SOCS-2, Traf5, DAGKα, LDHAα,

phosphoglycerate mutase, CD98, 4-IBB-L, and FasL.

22. The method of claim 12, wherein the anergy marker is GBP-3.

23. A method of screening for test compounds capable of inhibiting an immune disorder, the method comprising: a) contacting a panel of anergy marker proteins with a plurality of test compounds, wherein the panel of anergy marker proteins comprise at least 2 anergy marker proteins encoded by anergy markers listed in Group I or Group II or Group III or Group IV; b) detecting binding of one of the test compounds to the panel of anergy marker proteins, relative to other test compounds; and c) correlating the amount of binding of the test compound to the panel of anergy marker proteins with the ability of the test compound to inhibit an immune disorder, wherein binding indicates that the test compound is capable of inhibiting an immune disorder.

24. The method of claim 23, wherein the method of screening is high-throughput screening.

25. The method of claim 23, wherein the test compound is from a library selected from a group of libraries consisting of spatially addressable parallel solid phase or solution phase libraries or synthetic libraries made from deconvolution, `one-bead one-compound` methods and by affinity chromatography selection.

26. The method of claim 23, wherein the selected test compound prevents binding of the anergy marker protein with a bioactive agent selected from the group consisting of naturally-occurring compounds, biomolecules, proteins, **peptides**, oligopeptides, polysaccharides, nucleotides and polynucleotides.

27. The method of claim 23, wherein the test compound is a bioactive agent selected from the group consisting of naturally-occurring compounds, biomolecules, proteins, **peptides**, oligopeptides, polysaccharides, nucleotides and polynucleotides.

28. The method of claim 23, wherein the test compound is a small molecule.

29. The method of claim 23, wherein the anergy marker is selected from the group consisting of Msa.21745.0_s_at (also Mm. 21985), Hs. 129764, U44731_s_at (also Mm. 1909), Hs. 240849, Msa.1669.0_f_at (also Mm. 19123), and GenBank PID:g2853176.

30. The method of claim 23, wherein the anergy marker is selected from the group consisting of Mm. 116802, Hs. 248037, Mm. 10085 and Hs. 96149.

31. The method of claim 23, wherein the anergy marker is selected from the group consisting of Z31202_s_at, aa144045_s_at, aa174748_at c81206_rc_at, D86609_s_at, ET63436_at k00083_s_at, MIP1-B_at Msa.11439.0_s_at, Msa.15983.0_f_at, Msa.1669.0_f_at, Msa.18713.0_g_at, U44731_s_at, x12531_s_at, and x67914_s_at.

32. The method of claim 23, wherein the anergy marker is selected from the group consisting of GRG4, jumonji, RPTPσ, PTP-1B, RPTPκ, GBP-3, Rab10, caspase-3, SOCS-2, Traf5, DAGKα, LDHAα, phosphoglycerate mutase, CD98, 4-IBB-L, and FasL.

33. The method of claim 23, wherein the anergy marker is GBP-3.

34. The method of claim 23, wherein the immune disorder is selected from the group consisting of T cell disorders, B cell disorders, autoimmune disorders, infectious disorders, proliferative disorders, transplant rejection and cancer.

35. The method of claim 23, wherein the immune disorder is selected from

the group consisting of diabetes mellitus, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, multiple sclerosis, encephalomyelitis, myasthenia gravis, systemic lupus erythematosis, autoimmune thyroiditis, atopic dermatitis eczematous dermatitis, psoriasis, Sjogren's Syndrome, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Graves' disease, sarcoidosis, primary biliary cirrhosis, uveitis posterior, interstitial lung fibrosis, graft-versus-host disease, and allergy.

36. The method of claim 23, wherein the immune disorder is selected from the group consisting of diabetes mellitus, rheumatoid arthritis, multiple sclerosis, Crohn's disease, asthma, allergic asthma, graft-versus-host disease, and allergy.

37. The method of claim 23, wherein the cancer is selected from the group consisting of lung cancer, breast cancer, lymphoid cancer, gastrointestinal cancer, genitourinary tract cancer, pharynx cancer, colon cancer, renal-cell carcinoma, prostate cancer, testicular cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

38. The method of claim 23, wherein the cancer is selected from the `group consisting of breast cancer, renal cell carcinoma, melanoma, lymphoma, and multiple myeloma.

39. A method of screening test compounds for inhibitors of an immune disorder in a subject, the method comprising the steps of: a) obtaining a sample comprising cells; b) contacting an aliquot of the sample with one of a plurality of test compounds; c) comparing a level of expression of an anergy marker listed in Group I or Group II or Group III or Group IV; and d) selecting one of the test compounds which substantially modulates the level of expression of the anergy marker in the aliquot containing that test compound, relative to other test compounds.

40. The method of claim 39, wherein the test compound is from a library selected from a group of libraries consisting of spatially addressable parallel solid phase or solution phase libraries or synthetic libraries made from deconvolution, `one-bead one-compound` methods and by affinity chromatography selection.

41. The method of claim 39, wherein the anergy marker is selected from the group consisting of Msa.21745.0_s_at (also Mm. 21985), Hs. 129764,

19123), and GenBank PID:g2853176.

42. The method of claim 39, wherein the anergy marker is selected from the group consisting of Z31202_s_at, aa144045_s_at, aa174748_at, c81206_rc_at, D86609_s_at, ET63436_at, k00083_s_at, MIP1-B_at, Msa.11439.0_s_at, Msa.15983.0_f_at, Msa.1669.0_f_at, Msa.18713.0_g_at, U44731_s_at, x12531_s_at, and x67914_s_at.

43. The method of claim 39, wherein the anergy marker is selected from the group consisting of Mm. 116802, Hs. 248037, M. 10085 and Hs. 96149.

44. The method of claim 39, wherein the anergy marker is selected from the group consisting of GRG4, jumonji, RPTPσ, PTP-1B, RPTPκ, GBP-3, Rab10, caspase-3, SOCS-2, Traf5, DAGKα, LDHAα, phosphoglycerate mutase, CD98, 4-IBB-L, and FasL.

45. The method of claim 39, wherein the anergy marker is GBP-3.

L12 ANSWER 19 OF 38 USPATFULL on STN

2003:89463 **T cell receptor** Vβ-Dβ-Jβ sequence and methods for its detection.

Zhang, Jingwu Z., Missouri City, TX, United States
Baylor College of Medicine, Houston, TX, United States (U.S. corporation)
US 6541608 B1 20030401
APPLICATION: US 2000-641576 20000818 (9)
PRIORITY: US 1999-121311P 19990223 (60)
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In one embodiment, the present invention is directed to a first oligonucleotide comprising the sequence of or derived from 5'-CTAGGGCGGGCGGGACTCACCTAC-3' or the nucleic acid sequence complementary thereto. The first oligonucleotide can be used with a nucleic acid of between 15 and 30 nucleotides that does not comprise the sequence of the first oligonucleotide and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **V**β13.1 T cells, wherein the sequences of the oligonucleotide and the nucleic acid are not found on the same strand of the **V**β13.1 gene pair, to amplify a portion of the **V**β13.1 gene. Alternatively, the first oligonucleotide can be used with a labeling moiety in methods of detecting a LGRAGLTY motif found in T cell receptors of **V**β13.1 T cells. This motif is associated with autoimmune diseases, such as multiple sclerosis (MS). Once the motif is detected, the autoimmune disease can be treated or its progress monitored. The autoimmune disease can be treated by administering one or more **peptides** comprising the LGRAGLTY motif.

CLM What is claimed is:

1. A **peptide** of from 8 to approximately 32 amino acids which comprises the sequence of SEQ ID NO:3.

2. The **peptide** of claim 1 which comprises amino acids 2-21 of SEQ ID NO:32.

3. The **peptide** of claim 1 which consists of amino acids 2-21 of SEQ ID NO:32.

4. The **peptide** of claim 1 which consists of the sequence of SEQ ID NO:3.

L12 ANSWER 20 OF 38 USPATFULL on STN

2003:78489 Novel complex-forming proteins.

Jerome, Valerie, Coelbe, GERMANY, FEDERAL REPUBLIC OF
Sedlacek, Hans-Harald, Marburg, GERMANY, FEDERAL REPUBLIC OF
Mueller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF

APPLICATION: US 2002-201949 A1 20020725 (10)
PRIORITY: DE 2000-19900743 20000112
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a complex of specifically complex-forming proteins which are not naturally occurring, comprising the following components: a) at least one ligand specific for a target structure, b) at least one protein comprising a mutated dimerization domain, the mutated dimerization domain having been derived by mutation of a naturally occurring dimerization domain, it being possible for this mutated dimerization domain to interact specifically with component c) and the component b) being connected covalently to the component a), c) at least one protein comprising a mutated dimerization domain, the mutated dimerization domain having been derived by mutation of a naturally occurring dimerization domain, it being possible for this mutated dimerization domain to interact specifically with component b) and the component c) is linked covalently to the component d), and d) at least one effector. In addition, the invention relates to the use and preparation of these complexes, and to nucleic acid constructs coding for the proteins mentioned and use thereof.
CLM What is claimed is:

1. A complex comprising the following components: a) at least one ligand specific for a target structure; b) at least one protein comprising a mutated dimerization domain obtained by mutation of a naturally occurring dimerization domain, wherein said mutated dimerization domain binds specifically with component c) and said component b) is covalently bonded to said component a); c) at least one protein comprising a mutated dimerization domain obtained by mutation of a naturally occurring dimerization domain, wherein said mutated dimerization domain binds specifically with said component b) and said component c) is covalently bonded to component d); and d) at least one effector; wherein said components b) and c) are not naturally occurring proteins.

2. The complex as claimed in claim 1, wherein said component a) is replaced by said component d).

3. The complex as claimed in claim 1, wherein said component d) is replaced by said component a).

4. The complex as claimed in claim 1, which further comprises a fusogenic **peptide** or a translocalization **peptide**.

5. The complex as claimed in claim 1, which further comprises a cleavage sequence for a protease between said components c) and d) or a) and b).

6. The complex as claimed in claim 1, wherein said component a) is selected from the group consisting of: a growth factor, a cytokine, TNF, a chemokine, a **peptide** hormone, a mediator, a steroid hormone, a vitamin, a complement factor, a clotting factor, a kinin system factor, a fibrinolysis system factor, a plasmatic enzyme, a cell enzyme, a plasmatic enzyme inhibitor, a cell enzyme inhibitor, a virus coat protein, a cell receptor for the afore-mentioned molecules, an antibody, an antibody cleavage product, a DNA binding protein, a DNA binding domain of a transcription factor and an activation domain of a transcription factor.

7. The complex as claimed in claim 1, wherein said components b) and c) are obtained by mutating the naturally occurring dimerization domains of proteins which bind naturally to one another.

8. The complex as claimed in claim 7, wherein said naturally occurring dimerization domains of components b) and c) are selected from the group of naturally dimerizing partners consisting of:

Fos	Jun or Jun B or Jun D;
FRAU-1	Jun or Jun B or Jun D;
FRAU-2	Jun or Jun B or Jun D;
FOS-B	Jun or Jun B or Jun D;
OCT-1	Jun or Jun B or Jun D;
NFKB (p 65)	IKB;
Ras	RAF;
CD4	p56LcK;
bcl-2	bad or bax;
Cyclin A	cdkl;
E2F	DP;
CD40	CD40L;
Myc	Max;
Myc N	Max;
Myc L	Max;
p 105 (Rbl)	AFF-2, E1A;
p 107 (Rb2)	E7, E2F or Myc;
p 130	E7, E2F or Myc;
CBL	Gag;
TRP	TRP;
Met	Met;
Myb	p 67 or p 160;
VAV	p 67 or p 160;
APC	α- or β-Catenin;
APC	APC;
VD receptor	h-(Retinoid x-receptor) RXR α or β;
T3 receptor	HRXR α or β;
MyoD	E12;
E12	Id;
E47	Id;
HHSP90	Progesterone receptor;
HHSP90	Glucocorticoid receptor;
HHSP90	Mineralocorticoid receptor;
HHSP90	Dioxin receptor;
Dioxin receptor	Arnt;
HPS90	FKBP59;
HSP90	Cyclosporin-binding protein;
HPS90	$Pp60^{V\text{-}src}$
HSP70	HSF1 heat shock factor 1; and
HSP70	HSF2 heat shock factor 2.

9. The complex as claimed in claim 8, wherein said naturally dimerizing partners belong to the helix-loop-helix/leucine zipper family of proteins.

10. The complex as claimed in one of claim 7, wherein said mutated dimerization domains are obtained by inserting: 3-18 cysteines in said naturally occurring dimerization domain in at least one of said proteins of component b) and in at least one of said proteins of component c); 3-24 basic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component b) and 3-24 acidic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component c); 3-24 basic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component c) and 3-24 acidic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component b); 3-24 hydrophobic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component b) and 3-24 aromatic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component c); 3-24 hydrophobic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component c) and 3-24 aromatic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component b); and/or 3-24 aromatic amino acids in said naturally

occurring dimerization domain in at least one of said proteins of component b) and 3-24 aromatic amino acids in said naturally occurring dimerization domain in at least one of said proteins of component c).

11. The complex as claimed in claim 10, in which said components b) and c) are mutated binding domains of c-fos and c-jun, comprising the following mutations:

c-fos amino acid	167 E → K
	172 E → K
	181 E → K
c-jun amino acid	283 K → E
	288 K → E
	302 K → E

12. The complex as claimed in claim 1, wherein said component d) is selected from the group consisting of: inhibitors of cell proliferation, apoptosis-inducing proteins, cytostatic proteins, cytotoxic proteins, coagulation-inducing factors, angiogenesis-inducing factors, angiogenesis-inhibiting factors, growth factors, cytokines, chemokines, interleukins, interferons, complement factors, clotting factors, fibrinolysis-inducing proteins, **peptide** hormones, mediators, bacterial proteins, receptors, viral antigens, parasitic antigens, tumor antigens, autoantigens, tissue antigens, adhesion molecules, antibodies, antibody cleavage products, enzymes for reacting with a signal-emitting component, enzymes for converting a precursor of an active substance into an active substance, fluorescent dyes, isotopes, metal-binding proteins, and a DNA-binding domain.

13. A method for treating diseased cells, wherein said disease results from inflammation, autoimmune diseases, defective formation of blood cells, nervous system damage, blood-clotting system disorders, blood circulation system disorders, tumor formation, viral infections, or bacterial infections, comprising administering said complex of claim 1 to said cells.

14. A method for introducing a vector into a cell of an organism or cell culture, comprising binding said complex of claim 1 to a viral or nonviral vector and introducing said vector into said cell of an organism or a cell culture in a cell-specific manner.

15. A method of detecting the presense or amount of a reactant in vitro or in vivo, comprising contacting said complex of claim 1 with said reactant, either in vivo or in vitro, wherein said component a) binds to said reactant and said component d) emits a signal, such that the presence or amount of said reactant is detected by measuring the amount of said emitted signal.

16. A nucleic acid construct coding for a protein of claim 1.

17. The nucleic acid construct as claimed in claim 16, coding for an activator subunit of an activator-responsive promoter unit.

18. A host cell comprising said nucleic acid construct as claimed in claim 16.

19. The host cell as claimed in claim 18, selected from the group consisting of a bacterium, a yeast and a mammalian cell.

20. A method of expressing a protein of claim 1, comprising expressing a nucleic acid encoding said protein in a host cell under conditions such that said protein is expressed in a detectable amount.

21. A method of producing a complex between said component b) and said

components b), as claimed in claim 1, comprising: (a) expressing said at least one protein of said component b) by translating a nucleic acid construct encoding said protein; (b) expressing said at least one protein of said component c) by translating a nucleic acid construct encoding said protein; (c) isolating said proteins of steps (a) and (b); (d) contacting said at least one protein of step a) with said at least one protein of step b) under conditions such that said proteins bind to one another.

22. The complex as claimed in claim 6, wherein said antibody cleavage product is selected from the group consisting of: $F(ab)_2$, a single-chain Fv, a single-chain, a double antigen-binding molecule, and an Fc fragment.

23. The complex as claimed in claim 12, wherein said receptor is selected from the group consisting of receptors for: growth factors, cytokines, chemokines, interleukins, interferons, complement factors, clotting factors, fibrinolysis-inducing proteins, **peptide** hormones, steroid hormones, mediators, and virus coat proteins.

24. The complex as claimed in claim 12, wherein said antibody cleavage product is selected from the group consisting of: $F(ab)_2$, Fab, single-chain Fv, and single-chain double antigen-binding proteins.

25. A vaccine comprising the complex as claimed in claim 1.

26. A complex comprising the following components: a) at least one ligand specific for a target structure; b) at least one protein comprising a mutated dimerization, wherein said mutated dimerization domain binds specifically with component c) and said component b) is covalently bonded to said component a); c) at least one protein comprising a mutated dimerization domain, wherein said mutated dimerization domain binds specifically with said component b) and said component c) is covalently bonded to component d); and d) at least one effector; wherein said components b) and c) are not naturally occurring proteins.

27. The complex as claimed in claim 1, wherein at least one protein of component b) binds specifically with at least one protein of component c) with a binding constant of at least a K_M of 10^{-7} mol l^{-1}.

L12 ANSWER 21 OF 38 USPATFULL on STN
2003:64286 Methods of preventing or treating inflammatory or autoimmune disorders by administering CD2 antagonists in combination with other prophylactic or therapeutic agents.
Dingivan, Christine, Germantown, MD, UNITED STATES
US 2003044406 A1 20030306
APPLICATION: US 2002-91313 A1 20020304 (10)
PRIORITY: US 2001-273098P 20010302 (60)
US 2001-346918P 20011019 (60)
US 2002-358424P 20020219 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides to methods of preventing, treating or ameliorating an autoimmune or inflammatory disorder or one or more symptoms thereof utilizing combinatorial therapy. In particular, the present invention provides methods of preventing, treating, or ameliorating an autoimmune or inflammatory disorder or one or more symptoms thereof comprising administering to a subject in need thereof one or more CD2 antagonists and at least one other prophylactic or therapeutic agent. The present invention also provides compositions and articles of manufacture for use in preventing, treating or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder.

What is claimed is:

1. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof and a therapeutically effective amount of another, different CD2 binding molecule.

2. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of one or more CD2 binding molecules and a therapeutically effective amount of one or more immunomodulatory agents.

3. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof and a therapeutically effective amount of one or more immunomodulatory agents.

4. A method of treating psoriasis or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of one or more CD2 binding molecules and a therapeutically effective amount of one or more dermatological agents.

5. A method of treating psoriasis or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of MEDI-507 and a therapeutically effective amount of one or more dermatological agents.

6. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of one or more CD2 binding molecules and a therapeutically effective amount of one or more anti-angiogenic agents.

7. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof and a therapeutically effective amount of one or more anti-angiogenic agents.

8. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of a first CD2 binding molecule and a therapeutically effective amount of a second, different CD2 binding molecule, wherein administration of the therapeutically effective amount of the first CD2 binding molecule results in the first CD2 binding molecule binding to at least 30% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes after the administration of the first CD2 binding molecule and prior to the administration of the second CD2 binding molecule.

9. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of a first CD2 binding molecule and a therapeutically effective amount of a second, different CD2 binding molecule, wherein administration of the therapeutically effective amount of the first CD2 binding molecule results in a mean absolute lymphocyte count of approximately 500 cells/mm^3 to below 1200 cells/mm^3 and administration of the therapeutically effective amount of the second, different CD2 binding molecule maintains a mean absolute lymphocyte count of approximately 500 cells/mm^3 to below 1200 cells/mm^3.

10. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of a first CD2 binding molecule and a therapeutically effective amount of a second, different CD2 binding molecule, wherein the therapeutically effective amount of the first CD2 binding molecule results in at least 30% of the CD2 **polypeptides** expressed by peripheral blood lymphocytes being bound to CD2 binding molecules after the administration of the first CD2 binding molecule and the administration of the therapeutically effective amount of the second, different CD2 binding molecule restores at least 30% of the CD2 **polypeptides** expressed by lymphocytes being bound by CD2 binding molecules.

11. A method of treating an autoimmune disorder or inflammatory disorder or ameliorating one or more symptoms thereof, said method comprising administering to a subject in need thereof a therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof and a therapeutically effective amount of one or more anti-inflammatory agents.

12. The method of claim 8, 9 or 10, wherein the first CD2 binding molecule is an anti-CD2 antibody that immunospecifically binds to a CD2 **polypeptide**.

13. The method of claim 8, 9 or 10, wherein the first CD2 binding molecule is a fusion protein that immunospecifically binds to a CD2 **polypeptide**.

14. The method of claim 8, 9 or 10, wherein the second CD2 binding molecule is a fusion protein that immunospecifically binds to a CD2 **polypeptide**.

15. The method of claim 12, wherein the second CD2 binding molecule is a fusion protein that immunospecifically binds to a CD2 **polypeptide**.

16. The method of claim 8, 9 or 10, wherein the second CD2 binding molecule is an anti-CD2 antibody that immunospecifically binds to a CD2 **polypeptide**.

17. The method of claim 13, wherein the second CD2 binding molecule is an anti-CD2 antibody that immunospecifically binds to a CD2 **polypeptide**.

18. The method of claim 12, wherein the antibody is a monoclonal antibody.

19. The method of claim 16, wherein the antibody is a monoclonal antibody.

20. The method of claim 18, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

21. The method of claim 19, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

22. The method of claim 12, wherein the anti-CD2 antibody is LoCD2a/BTI-322 or MEDI-507.

23. The method of claim 16, wherein the anti-CD2 antibody is LoCD2a/BTI-322 or MEDI-507.

24. The method of claim 13, wherein the fusion protein is LFA3TIP.

25. The method of claim 14, wherein the fusion protein is LFA3TIP.

26. The method of claim 2, 4 or 6, wherein at least one CD2 binding

molecule is an anti-CD2 antibody that immunospecifically binds to a CD2 **polypeptide**.

27. The method of claim 26, wherein the antibody is a monoclonal antibody.

28. The method of claim 27, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

29. The method of claim 2, 4 or 6, wherein at least one CD2 binding molecule is a fusion protein that immunospecifically binds to a CD2 **polypeptide**.

30. The method of claim 29, wherein the fusion protein is LFA3TIP.

31. The method of claim 2, 4 or 6, wherein the CD2 binding molecules are administered to said subject parenterally.

32. The method of claim 8, 9 or 10, wherein the first and second CD2 binding molecule are administered to said subject parenterally.

33. The method of claim 1, 3, 5, 7 or 11, wherein MEDI-507 is administered to said subject parenterally.

34. The method of claim 2, 4 or 6, wherein said effective amount of one or more CD2 binding molecules is a dose ranging from 0.5 to 100 μg/kg.

35. The method of claim 2, 4 or 6, wherein said effective amount of one or more CD2 binding molecules is a unit dose of 0.1 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg or 15 mg.

36. The method of claim 2, 4 or 6, wherein said effective amount of one or more CD2 binding molecules is a unit dose of between 0.1 mg and 20 mg.

37. The method of claim 2, 4 or 6, wherein said effective amount of the first and the second CD2 binding molecules is a dose of between 0.5 and 100 μg/kg.

38. The method of claim 8, 9 or 10, wherein said effective amount of the first and the second CD2 binding molecules is a unit dose of 0.1 mg, 0.25 mg. 0.4 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg or 15 mg

39. The method of claim 2, 4 or 6, wherein at least one CD2 binding molecule does not inhibit the interaction between a CD2 **polypeptide** and LFA-3.

40. The method of claim 1, 8, 9 or 10, wherein said effective amount of MEDI-507 is a unit dose of 0.1 mg, 0.25 mg. 0.4 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg or 15 mg.

41. The method of claim 4 or 5, wherein at least one dermatological agent is a topical agent.

42. The method of claim 41, wherein the topical agent is an emolliment, salicyclic acid, coal tar, a topical steroid, a topical corticosteroid, a topical vitamin D3 analog, tazarotene, or a topical retinoid.

43. The method of claim 4 or 5, wherein at least one dermatological agent is phototherapy.

44. The method of claim 2 or 3, wherein at least one immunomodulatory

agent is a small organic molecule.

45. The method of claim 2 or 3 wherein at least one immunomodulatory agent is a **T cell receptor** modulator or a cytokine receptor modulator.

46. The method of claim 44, wherein the small organic molecule is methotrexate, leflunomide, cyclophosphamide, cyclosporine A, FK506, mycophenolate mofetil, rapamycin, mizoribine, deoxyspergualin, brequinar, a malononitriloamide, a steroid or a corticosteriod.

47. The method of claim 45, wherein the **T cell receptor** modulator is an antibody, **peptide** or a fusion protein which immunospecifically binds to a **T cell receptor**.

48. The method of claim 47, wherein the antibody that immunospecifically binds to a **T cell receptor** is a monoclonal antibody or an antigen-binding fragment thereof.

49. The method of claim 48, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

50. The method of claim 47, wherein the antibody is an anti-CD3 antibody, an anti-CD4 antibody, an anti-CD8 antibody, an anti-CD11a antibody, an anti-CD40 antibody, an anti-CD40L antibody, an anti-CD80 antibody or an anti-LFA1 antibody.

51. The method of claim 47, wherein the fusion protein is CTLA4-Ig.

52. The method of claim 45, wherein the cytokine receptor modulator is a cytokine, a fragment of a cytokine, a fusion protein or an antibody that immunospecifically binds to a cytokine receptor.

53. The method of claim 45, wherein the cytokine receptor modulator is a **peptide**, **polypeptide**, fusion protein or an antibody that immunospecifically binds to a cytokine.

54. The method of claim 52, wherein the antibody that immunospecifically binds to a cytokine receptor is a monoclonal antibody or an antigen-binding fragment thereof.

55. The method of claim 54, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

56. The method of claim 52, wherein the antibody is an anti-IL-2 receptor antibody or anti-IL-12 receptor antibody.

57. The method of claim 53, wherein the antibody that immunospecifically binds to a cytokine is a monoclonal antibody or an antigen-binding fragment thereof.

58. The method of claim 57, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

59. The method of claim 53, wherein the antibody is an anti-IL-1β antibody or an anti-IL-6 antibody.

60. The method of claim 52, wherein the cytokine is IL-4 or IL-10.

61. The method of claim 53, wherein the **polypeptide** is a fragment of a cytokine receptor that immunospecifically binds to a cytokine.

62. The method of claim 6 or 7, wherein at least one anti-angiogenic factor is angiostatin, a TNF-α antagonist, a VEGFR antagonist, an RGD containing **peptide**, or endostatin.

63. The method of claim 62, wherein the TNF-α antagonist is

64. The method of claim 11, wherein at least one anti-inflammatory agent is a non-steroidal anti-inflammatory drug.

65. The method of claim 64, wherein the non-steriodal anti-inflammatory drug is aspirin, ibuprofen, diclofenac, nabumetone, naproxen, or ketoproten.

66. The method of any one of claims 1-3 and 6-11, wherein the autoimmune disorder is rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's Syndrome, psoriasis, or lupus erythematosus.

67. The method of any one of claims 1-3 and 6-11, wherein the inflammatory disorder is asthma, encephilitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), arthritis, or an allergic disorder.

68. The method of claim 4 or 5, wherein the psoriasis is plaque psoriasis.

69. The method of any one of claims 1-11, wherein the subject is a human.

70. An article of manufacture comprising packaging material and a pharmaceutical composition in suitable form for administration to a human contained within said packaging material, wherein said pharmaceutical composition comprises MEDI-507 or an antigen-binding fragment thereof, another therapeutic factor and a pharmaceutically acceptable carrier.

71. The article of manufacture of claim 70 which further comprises instructions contained with said packaging material which suggests a dosing regimen for the prevention or treatment of an inflammatory disorder or an autoimmune disorder.

L12 ANSWER 22 OF 38 USPATFULL on STN
2003:57071 Compositions and methods for WT1 specific immunotherapy.
Gaiger, Alexander, Seattle, WA, UNITED STATES
Smithgall, Molly D., Seattle, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Cheever, Martin A., Mercer Island, WA, UNITED STATES
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Sutherland, R. Alec, Bothell, WA, UNITED STATES
Corixa Corporation, Seattle, WA, UNITED STATES (U.S. corporation)
US 2003039635 A1 20030227
APPLICATION: US 2002-125635 A1 20020416 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compositions comprise one or more of a WT1 polynucleotide, a WT1 **polypeptide**, an antigen-presenting cell presenting a WT1 **polypeptide**, an antibody that specifically binds to a WT1 **polypeptide**; or a T cell that specifically reacts with a WT1 **polypeptide**. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.
CLM What is claimed is:
1. A method for inducing an immune response in an animal, comprising: (a) providing a composition comprising a polynucleotide encoding at least an immunogenic portion of a WT1 **polypeptide**, wherein the polynucleotide has at least 90% identity to SEQ ID NO:452, 389, 453, and 381, and (b) administering said composition to the animal; thereby inducing an immune response in the animal.

2. The method of claim 1, wherein said composition further comprises a

component selected from the group consisting of a physiologically acceptable carrier and an adjuvant.

3. The method according to claim 1, wherein the WT1 polynucleotide is delivered by a viral based delivery system.

4. The method according to claim 3, wherein the viral based delivery system is an adenovirus.

5. The method according to claim 3, wherein the viral based delivery system is an alphavirus.

6. The method according to claim 1, wherein the WT1 polynucleotide is delivered as a naked DNA.

7. The method of claim 1, wherein the immune response induced is a CD8+ cytotoxic T lymphocyte response.

9. The method of claim 1, wherein the immune response induced is both a CD4+ T helper and CD8+ cytotoxic T cell immune response.

10. A method for treating a malignancy associated with WT1 expression in a patient, comprising administering to the patient a composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component comprising at least an immungenic portion of a WT1 **polypeptide**.

11. An isolated **polypeptide** comprising at least an immunogenic portion of the WT1 protein, wherein said **polypeptide** comprises the amino acid sequence set forth in SEQ ID NO:241.

12. The isolated **polypeptide** according to claim 11 wherein the **polypeptide** has been modified such that the ability of the **polypeptide** to bind to HLA-A2 is increased relative to that of the **polypeptide** set forth in SEQ ID NO:241.

13. The isolated **polypeptide** according to claim 12 wherein said **polypeptide** has increased immunogenicity relative to the **polypeptide** set forth in SEQ ID NO:241.

14. The isolated **polypeptide** according to claim 12 wherein said **polypeptide** comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NOs:414-450.

15. The isolated **polypeptide** according to claim 11 wherein the **polypeptide** has been modified such that the ability of the **polypeptide** to bind to HLA-A2 is increased relative to that of the **polypeptide** set forth in SEQ ID NO:241.

16. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 1 (PI) of SEQ ID NO:241

17. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 2 (P2) of SEQ ID NO:241.

18. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 4 (P4) of SEQ ID NO:241.

19. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 6 (P6) of SEQ ID NO:241.

20. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 8 (P8) of SEQ ID NO:241.

21. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 9 (P9) of SEQ ID NO:241.

22. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 1 (P 1) and position 4 (P4) of SEQ ID NO:241.

23. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 1 (P1) and position 9 (P9) of SEQ ID NO:241.

24. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 1 (P1), position 4 (P4), and position 9 (P9) of SEQ ID NO:241.

25. The isolated **polypeptide** according to claim 15 wherein said modification comprises a substitution at position 6 (P6) and position 9 (P9) of SEQ ID NO:241.

26. An isolated **polypeptide** comprising at least an immunogenic portion of a WT1 **polypeptide**, wherein said immunogenic portion comprises an amino acid sequence selected from the group consisting of: (i) a sequence set forth in SEQ ID NO:451; and (ii) a **polypeptide** selected from the group consisting of: (a) a sequence set forth in any one of SEQ ID NOs:414-450; (b) a sequence having at least 70% identity to a sequence set forth in any one of SEQ ID NOs:414-450; and (c) a sequence having at least 90% identity to a sequence set forth in any one of SEQ ID NOs:414-450; wherein the ability of the **polypeptide** to bind to HLA-A2 is increased relative to that of the **polypeptide** set forth in SEQ ID NO:241.

27. A method for inducing an immune response in a mammal, comprising: (a) providing a composition comprising a polynucleotide encoding the isolated **polypeptide** of claim 26; and (b) administering said polynucleotide to the mammal; thereby inducing an immune response in the mammal.

28. An expression vector comprising a polynucleotide of any one of the sequences set forth in SEQ ID NOs:452 and 453 or a polynucleotide encoding the isolated **polypeptide** of claim 26 operably linked to an expression control sequence.

29. A host cell transformed or transfected with an expression vector according to claim 28.

30. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of: (a) a **polypeptide** according to claim 26; (b) antigen-presenting cells pulsed with or that express a **polypeptide** according to claim 26, under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

31. An isolated T cell population, comprising T cells prepared according to the method of claim 30.

32. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of: (a) **polypeptides** according to claim 26; and (b) T cells according to claim 31.

33. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 32.

34. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 32.

35. An isolated **polypeptide** comprising an amino acid sequence of any one of SEQ ID NOs:454-455.

L12 ANSWER 23 OF 38 USPATFULL on STN
2003:10284 Recombinant MHC molecules useful for manipulation of antigen-specific T-cells.
Burrows, Gregory G., Portland, OR, UNITED STATES
Vandenbark, Arthur A., Portland, OR, UNITED STATES
US 2003007978 A1 20030109
APPLICATION: US 2001-847172 A1 20010501 (9)
PRIORITY: US 1997-64552P 19970916 (60)
US 1997-64555P 19971010 (60)
US 2000-200942P 20000501 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Two-domain MHC **polypeptides** useful for manipulation of antigen-specific T-cells are disclosed. These **polypeptides** include MHC class II-based molecules that comprise covalently linked β1 and α1 domains, and MHC class I-based molecules that comprise covalently linked α1 and α2 domains. These **polypeptides** may also include covalently linked antigenic determinants, toxic moieties, and/or detectable labels. The disclosed **polypeptides** can be used to target antigen-specific T-cells, and are useful, among other things, to detect and purify antigen-specific T-cells, to induce or activate T-cells, and to treat conditions mediated by antigen-specific T-cells.

CLM What is claimed is:

1. A purified MHC Class II **polypeptide** comprising covalently linked first and second domains, wherein: the first domain is a human MHC class II β1 domain and the second domain is a mammalian MHC class II α1 domain and wherein the amino terminus of the second domain is covalently linked to the carboxy terminus of the first domain and wherein the MHC class II molecule does not include an α2 or a β2 domain; or the first domain is a human MHC class I α1 domain and the second domain is a mammalian MHC class I α2 domain, and wherein the amino terminus of the second domain is covalently linked to the carboxy terminus of the first domain and wherein the MHC class I molecule does not include an α3 domain.

2. The **polypeptide** of claim 1 wherein the covalent linkage between the first and second domains is provided by a **peptide** linker sequence.

3. The **polypeptide** of claim 1 wherein the **polypeptide** further comprises, covalently linked to the amino terminus of the first domain, a third domain comprising an antigenic determinant.

4. The **polypeptide** of claim 3, wherein the antigenic determinant is a **peptide** antigen.

5. The **polypeptide** of claim 4, wherein the covalent linkage between the first and third domains is provided by a **peptide** linker sequence.

6. The **polypeptide** of claim 1, further comprising an antigenic determinant associated with the **polypeptide** by non-covalent interaction.

7. The **polypeptide** of claim 6, wherein the antigenic determinant is a **peptide** antigen.

8. The **polypeptide** of claim 1, wherein the **polypeptide** further comprises a covalently linked detectable marker or toxic moiety.

9. The **polypeptide** of claim 1, wherein the covalent linkage between the β1 and α1 domains is provided by a **peptide** linker sequence.

10. A nucleic acid molecule encoding the **polypeptide** of claim 1.

11. The nucleic acid of claim 10, operably linked to a promoter.

12. A vector comprising the nucleic acid of claim 10.

13. The vector of claim 12, wherein the vector is a viral vector.

14. A host cell transformed with the nucleic acid of claim 10.

15. A recombinant **polypeptide** comprising β1 and α1 domains of a human MHC class II molecule wherein the amino terminus of the α1 domain is covalently linked to the carboxy terminus of the β1 domain, and wherein the MHC class II molecule does not include an α2 domain or a β2 domain.

16. The recombinant **polypeptide** according to claim 15, wherein the **polypeptide** further comprises an antigenic determinant associated with the **polypeptide** by covalent or non-covalent interaction.

17. The recombinant **polypeptide** according to claim 16, wherein the antigenic determinant is covalently linked to the amino terminus of the β1 domain.

18. The recombinant **polypeptide** according to claim 15, wherein the **polypeptide** further comprises a detectable marker or toxic moiety.

19. A recombinant **polypeptide** comprising a human MHC class I α1 domain and a human MHC class I α2 domain, and wherein the amino terminus of the α2 domain is covalently linked to the carboxy terminus of the α1 domain, and wherein the MHC class I molecule does not include an α3 domain.

20. The recombinant **polypeptide** according to claim 19, wherein the **polypeptide** further comprises an antigenic determinant associated with the **polypeptide** by covalent or non-covalent interaction.

21. The recombinant **polypeptide** according to claim 20, wherein the antigenic determinant is covalently linked to the amino terminus of the α1 domain.

22. The recombinant **polypeptide** according to claim 20, wherein the **polypeptide** further comprises a detectable marker or toxic moiety.

23. A pharmaceutical composition comprising a **polypeptide** according to claim 1, and a pharmaceutically acceptable carrier.

24. A recombinant **polypeptide** comprising only two domains of a human MHC class II **peptide**, wherein the two domains are an a1 domain and a β1 domain, wherein the amino terminus of the a1 domain is covalently linked to the carboxy terminus of the β1 domain.

25. The **polypeptide** of claim 24, wherein the covalent linkage between the α1 and β1 domains is provided by a **peptide** linker sequence.

26. The purified MHC **polypeptide** of claim 24, wherein the MHC

polypeptide is non-covalently associated with an antigen.

27. The purified MHC **polypeptide** of claim 24, wherein the MHC **polypeptide** is covalently associated with an antigen.

28. A recombinant **polypeptide** comprising only two domains of a human MHC class I **peptide**, wherein the two domains are an α1 domain and a α2 domain, wherein the amino terminus of the α2 domain is covalently linked to the carboxy terminus of the α1 domain.

29. The **polypeptide** of claim 28, wherein the covalent linkage between the β1 and α2 domains is provided by a **peptide** linker sequence.

30. The purified MHC **polypeptide** of claim 28, wherein the MHC **polypeptide** is non-covalently associated with an antigen.

31. The purified MHC **polypeptide** of claim 28, wherein the MHC **polypeptide** is covalently associated with an antigen.

32. A recombinant nucleic acid molecule, comprising first, second and third regions represented by the formula Pr-B-A, wherein: Pr is a promoter sequence; B is a coding sequence that encodes a β1 domain of a human MHC class II molecule; and A is a coding sequence that encodes an a1 domain of a human MHC class II molecule; wherein Pr is operably linked to B, and B and A comprise a single open reading frame.

33. A recombinant nucleic acid molecule, comprising first, second, third and fourth regions represented by the formula Pr-P-B-A, wherein: Pr is a promoter sequence; P is a coding sequence that encodes a **peptide** antigen; B is a coding sequence that encodes a β1 domain of a human MHC class II molecule; and A is a coding sequence that encodes an α1 domain of a human MHC class II molecule; wherein Pr is operably linked to P, and P, B and A comprise a single open reading frame.

34. A recombinant nucleic acid molecule, comprising first, second and third regions represented by the formula Pr-B-A, wherein: Pr is a promoter sequence; B is a coding sequence that encodes an α1 domain of a mammalian MHC class I molecule; and A is a coding sequence that encodes an α2 domain of a mammalian MHC class I molecule; wherein Pr is operably linked to B, and B and A comprise a single open reading frame, and wherein the open reading frame does not encode an α3 domain of a mammalian MHC class I molecule.

35. A recombinant nucleic acid molecule, comprising first, second, third and fourth regions represented by the formula Pr-P-B-A, wherein: Pr is a promoter sequence; P is a coding sequence that encodes a **peptide** antigen; B is a coding sequence that encodes an α1 domain of a human MHC class I molecule; and A is a coding sequence that encodes an α2 domain of a human MHC class I molecule; wherein Pr is operably linked to P, and P, B and A comprise a single open reading frame, and wherein the open reading frame does not encode an α3 domain of a mammalian MHC class I molecule.

36. A method for detecting or quantifying in a biological sample the presence of T-cells having a receptor specific for a specified antigen, comprising: contacting the biological sample with a recombinant **polypeptide** comprising either (1) covalently linked β1 and α1 domains of a human MHC class II molecule wherein the carboxy terminus of the β1 domain is covalently linked to the amino terminus of the α1 domain, and further comprising the specified antigen bound in a **peptide** binding groove formed by the β1 and

the α1 domain, or (2) a recombinant **polypeptide** comprising covalently linked α1 and α2 domains of a human MHC class I molecule wherein the carboxy terminus of the α1 domain is covalently linked to the amino terminus of the α2 domain, wherein the **polypeptide** does not include an α3 domain of a human MHC class I molecule and wherein the **polypeptide** further comprises the specified antigen bound in a **peptide** binding groove formed by the α1 and the α2 domain; and detecting or quantifying the presence of specific binding of the recombinant **polypeptide** with said T-cells.

37. A method for reducing an immune response against an antigenic determinant in a subject, comprising: administering a therapeutically effective amount of the **polypeptide** of claim 3, or of a nucleic acid encoding the **polypeptide** of claim 3; and subsequently presenting the antigenic determinant to the subject, wherein administration of the **polypeptide** or the nucleic acid sequence reduces the immune response when the antigenic determinant is presented in the subject.

38. The method of claim 37, wherein the reduced immune response is a decrease in an influx or proliferation of a T cell, a macrophage, a B cell, or an NK cell.

39. The method of claim 37, wherein the reduced immune response is a reduction in the expression of a cytokine.

40. The method of claim 37, wherein the reduced immune response is an induction of a T suppressor cell response.

41. A method for inducing an immunoregulatory cell against an antigenic determinant, comprising administering a therapeutically effective amount of the **polypeptide** of claim 3 to the immunoregulatory cell; and subsequently presenting the antigenic determinant to the immunoregulatory cell; wherein the presentation of the antigenic determinant results in an induction of the immunoregulatory cell.

42. The method of claim 41, wherein the immunoregulatory cell reduces inflammation and cellular recruitment when the antigen is subsequently encountered with an immunogenic stimulus.

43. The method of claim 41, wherein the antigenic determinant is a tissue specific antigenic determinant.

44. The method of claim 41, wherein the immunoregulatory cell is induced as compared to a control.

45. The method of claim 41, wherein the immunoregulatory cell is in vivo.

46. The method of claim 41, wherein the immunoregulatory cell is in vitro.

47. A method for inducing the expression of a cytokine in a mammalian T cell, comprising contacting the T cell with an effective amount of the **polypeptide** of claim 3, thereby inducing the expression of the cytokine.

48. The method of claim 47, wherein the cytokine is IL-10.

49. The method of claim 47, wherein the cell is in vivo.

50. The method of claim 47, wherein the cell is in vitro.

51. A method of treating or preventing an immune-mediated disorder in a subject, comprising administering to the subject a therapeutically effective amount of the **polypeptide** of claim 3 or of a nucleic acid

encoding the **polypeptide** of claim 3, wherein subsequent presentation of the antigenic determinant to an immune cell of the subject results in treatment or prevention of the immune-mediated disorder.

52. The method of claim 51, wherein the immune-mediated disorder is rheumatoid arthritis, chronic beryllium disease, insulin-dependent diabetes mellitus, throiditis, inflammatory bowel disease, uveitus, polyarteritis, Multiple Sclerosis or Myasthenia Gravis.

53. A pharmaceutical composition comprising the **polypeptide** of claim 3 in a pharmaceutically acceptable carrier.

54. A method of treating a disease caused by antigen-specific T-cells, comprising administering to a patient a composition comprising a **polypeptide** according to claim 3, or a nucleic acid encoding the **polypeptide** of claim 3, thereby treating the disease.

55. A method of activating a T cell in a subject, comprising administering a therapeutically effective amount of the **polypeptide** of claim 3, thereby activating the T cell.

56. The method of claim 55, wherein the subject is human.

57. The method of claim 55, wherein the T cell produces IL-10.

58. The method of claim 55, wherein the antigenic determinant is an antigenic determinant from a tumor cell.

L12 ANSWER 24 OF 38 USPATFULL on STN
2002:344628 Compositions and methods for the detection, diagnosis and therapy of hematological malignancies.
Gaiger, Alexander, Seattle, WA, UNITED STATES
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Mannion, Jane, Seattle, WA, UNITED STATES
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APPLICATION: US 2001-796692 A1 20010301 (9)
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DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are methods and compositions for the detection, diagnosis, prognosis, and therapy of hematological malignancies, and in particular, human leukemias and lymphomas of the follicular, Hodgkin's and B cell and T cll non-Hodgkin's types. Disclosed are compositions, methods and kits for eliciting immune and T cell responses to specific malignancy-related antigenic **polypeptides** and antigenic **polypeptide** fragments thereof in an animal. Also disclosed are compositions and methods for use in the identification of cells and biological samples containing one or more hematological malignancy-related compositions, and methods for the detection and diagnosis of such diseases and affected cell types. Also disclosed are diagnostic and therapeutic kits, as well as methods for the diagnosis, therapy and/or prevention of a variety of leukemias and lymphomas.

CLM What is claimed is:
1. An isolated **peptide** or **polypeptide**, comprising at least a first

coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

2. The isolated **peptide** or **polypeptide** of claim 1, wherein said amino acid sequence is at least about 92% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

3. The isolated **peptide** or **polypeptide** of claim 2, wherein said amino acid sequence is at least about 94% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

4. The isolated **peptide** or **polypeptide** of claim 3, wherein said amino acid sequence is at least about 96% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

5. The isolated **peptide** or **polypeptide** of claim 4, wherein said amino acid sequence is at least about 98% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

6. The isolated **peptide** or **polypeptide** of claim 4, wherein said amino acid sequence is at least about 99% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

7. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an at least about 50 contiguous amino acid sequence from any one of SEQ ID NO:669 to SEQ ID NO:2532.

8. The isolated **peptide** or **polypeptide** of claim 7, wherein said at least a first isolated coding region comprises an at least about 75 contiguous amino acid sequence from any one of SEQ ID NO:669 to SEQ ID NO:2532.

9. The isolated **polypeptide** of claim 8, wherein said at least a first isolated coding region comprises an at least about 100 contiguous amino acid sequence from any one of SEQ ID NO:669 to SEQ ID NO:2532.

10. The isolated **polypeptide** of claim 9, wherein said at least a first isolated coding region comprises an at least about 125 contiguous amino acid sequence from any one of SEQ ID NO:669 to SEQ ID NO:2532.

11. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

12. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 93% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:1380.

13. The isolated **peptide** or **polypeptide** of claim 12, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 96% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:1380.

14. The isolated **peptide** or **polypeptide** of claim 13, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 99% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:1380.

15. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 93% identical to the amino acid sequence of any one of SEQ ID NO:1381 to SEQ ID NO:1859.

16. The isolated **peptide** or **polypeptide** of claim 15, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 96% identical to the amino acid sequence of any one of SEQ ID NO:1381 to SEQ ID NO:1859.

17. The isolated **peptide** or **polypeptide** of claim 16, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 99% identical to the amino acid sequence of any one of SEQ ID NO:1381 to SEQ ID NO:1859.

18. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 93% identical to the amino acid sequence of any one of SEQ ID NO:1860 to SEQ ID NO:2105.

19. The isolated **peptide** or **polypeptide** of claim 18, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 96% identical to the amino acid sequence of any one of SEQ ID NO:1860 to SEQ ID NO:2105.

20. The isolated **peptide** or **polypeptide** of claim 19, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 99% identical to the amino acid sequence of any one of SEQ ID NO:1860 to SEQ ID NO:2105.

21. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 93% identical to the amino acid sequence of any one of SEQ ID NO:2106 to SEQ ID NO:2375.

22. The isolated **peptide** or **polypeptide** of claim 21, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 96% identical to the amino acid sequence of any one of SEQ ID NO:2106 to SEQ ID NO:2375.

23. The isolated **peptide** or **polypeptide** of claim 22, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 99% identical to the amino acid sequence of any one of SEQ ID NO:2106 to SEQ ID NO:2375.

24. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 93% identical to the amino acid sequence of any one of SEQ ID NO:2376 to SEQ ID NO:2532.

25. The isolated **peptide** or **polypeptide** of claim 24, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 96% identical to the amino acid sequence of any one of SEQ ID NO:2376 to SEQ ID NO:2532.

26. The isolated **peptide** or **polypeptide** of claim 25, wherein said at least a first isolated coding region comprises an amino acid sequence that is at least about 99% identical to the amino acid sequence of any one of SEQ ID NO:2376 to SEQ ID NO:2532.

27. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:669, SEQ ID NO:670, SEQ ID NO:671, SEQ ID NO:672, SEQ ID NO:673, SEQ ID NO:674, SEQ ID NO:675, SEQ ID NO:676, SEQ ID NO:677, SEQ ID NO:678, SEQ ID NO:679, SEQ ID NO:680, SEQ ID NO:681, SEQ ID NO:682, SEQ ID NO:683, SEQ ID NO:684, SEQ ID NO:685, SEQ ID NO:686, SEQ ID NO:687, SEQ ID NO:688, SEQ ID NO:689, SEQ ID NO:690, SEQ ID NO:691, SEQ ID NO:692, SEQ ID NO:693, SEQ ID NO:694, SEQ ID NO:695, SEQ ID NO:696, SEQ ID NO:697, SEQ ID NO:698, SEQ ID NO:699, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:705, SEQ ID NO:706, SEQ ID NO:707, SEQ ID

ID NO:713, SEQ ID NO:714, SEQ ID NO:715, SEQ ID NO:716, SEQ ID NO:717, SEQ ID NO:718, SEQ ID NO:719, SEQ ID NO:720, SEQ ID NO:721, SEQ ID NO:722, SEQ ID NO:723, SEQ ID NO:724, SEQ ID NO:725, SEQ ID NO:726, SEQ ID NO:727, SEQ ID NO:728, SEQ ID NO:729, SEQ ID NO:730, SEQ ID NO:731, SEQ ID NO:732, SEQ ID NO:733, SEQ ID NO:734, SEQ ID NO:735, SEQ ID NO:736, SEQ ID NO:737, SEQ ID NO:738, SEQ ID NO:739, SEQ ID NO:740, SEQ ID NO:741, SEQ ID NO:742, SEQ ID NO:743, SEQ ID NO:744, SEQ ID NO:745, SEQ ID NO:746, SEQ ID NO:747, SEQ ID NO:748, SEQ ID NO:749, SEQ ID NO:750, SEQ ID NO:751, SEQ ID NO:752, SEQ ID NO:753, SEQ ID NO:754, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID NO:759, SEQ ID NO:760, SEQ ID NO:761, SEQ ID NO:762, SEQ ID NO:763, SEQ ID NO:764, SEQ ID NO:765, SEQ ID NO:766, SEQ ID NO:767, SEQ ID NO:768, SEQ ID NO:769, SEQ ID NO:770, SEQ ID NO:771, SEQ ID NO:772, SEQ ID NO:773, SEQ ID NO:774, SEQ ID NO:775, SEQ ID NO:776, SEQ ID NO:777, SEQ ID NO:778, SEQ ID NO:779, SEQ ID NO:780, SEQ ID NO:781, SEQ ID NO:782, SEQ ID NO:783, SEQ ID NO:784, SEQ ID NO:785, SEQ ID NO:786, SEQ ID NO:787, SEQ ID NO:788, SEQ ID NO:789, SEQ ID NO:790, SEQ ID NO:791, SEQ ID NO:792, SEQ ID NO:793, SEQ ID NO:794, SEQ ID NO:795, SEQ ID NO:796, SEQ ID NO:797, SEQ ID NO:798, SEQ ID NO:799, SEQ ID NO:800, SEQ ID NO:801, SEQ ID NO:802, SEQ ID NO:803, SEQ ID NO:804, SEQ ID NO:805, SEQ ID NO:806, SEQ ID NO:807, SEQ ID NO:808, SEQ ID NO:809, SEQ ID NO:810, SEQ ID NO:811, SEQ ID NO:812, SEQ ID NO:813, SEQ ID NO:814, SEQ ID NO:815, SEQ ID NO:816, SEQ ID NO:817, SEQ ID NO:818, SEQ ID NO:819, SEQ ID NO:820, SEQ ID NO:821, SEQ ID NO:822, SEQ ID NO:823, SEQ ID NO:824, SEQ ID NO:825, SEQ ID NO:826, SEQ ID NO:827, SEQ ID NO:828, SEQ ID NO:829, SEQ ID NO:830, SEQ ID NO:831, SEQ ID NO:832, SEQ ID NO:833, SEQ ID NO:834, SEQ ID NO:835, SEQ ID NO:836, SEQ ID NO:837, SEQ ID NO:838, SEQ ID NO:839, SEQ ID NO:840, SEQ ID NO:841, SEQ ID NO:842, SEQ ID NO:843, SEQ ID NO:844, SEQ ID NO:845, SEQ ID NO:846, SEQ ID NO:847, SEQ ID NO:848, SEQ ID NO:849, SEQ ID NO:850, SEQ ID NO:851, SEQ ID NO:852, SEQ ID NO:853, SEQ ID NO:854, SEQ ID NO:855, SEQ ID NO:856, SEQ ID NO:857, SEQ ID NO:858, SEQ ID NO:859, SEQ ID NO:860, SEQ ID NO:861, SEQ ID NO:862, SEQ ID NO:863, SEQ ID NO:864, SEQ ID NO:865, SEQ ID NO:866, SEQ ID NO:867, SEQ ID NO:868, SEQ ID NO:869, SEQ ID NO:870, SEQ ID NO:871, SEQ ID NO:872, SEQ ID NO:873, SEQ ID NO:874, SEQ ID NO:875, SEQ ID NO:876, SEQ ID NO:877, SEQ ID NO:878, SEQ ID NO:879, SEQ ID NO:880, SEQ ID NO:881, SEQ ID NO:882, SEQ ID NO:883, SEQ ID NO:884, SEQ ID NO:885, SEQ ID NO:886, SEQ ID NO:887, SEQ ID NO:888, SEQ ID NO:889, SEQ ID NO:890, SEQ ID NO:891, SEQ ID NO:892, SEQ ID NO:893, SEQ ID NO:894, SEQ ID NO:895, SEQ ID NO:896, SEQ ID NO:897, SEQ ID NO:898, SEQ ID NO:899, SEQ ID NO:900, SEQ ID NO:901, SEQ ID NO:902, SEQ ID NO:903, SEQ ID NO:904, SEQ ID NO:905, SEQ ID NO:906, SEQ ID NO:907, SEQ ID NO:908, SEQ ID NO:909, SEQ ID NO:910, SEQ ID NO:911, SEQ ID NO:912, SEQ ID NO:913, SEQ ID NO:914, SEQ ID NO:915, SEQ ID NO:916, SEQ ID NO:917, SEQ ID NO:918, SEQ ID NO:919, SEQ ID NO:920, SEQ ID NO:921, SEQ ID NO:922, SEQ ID NO:923, SEQ ID NO:924, SEQ ID NO:925, SEQ ID NO:926, SEQ ID NO:927, SEQ ID NO:928, SEQ ID NO:929, SEQ ID NO:930, SEQ ID NO:931, SEQ ID NO:932, SEQ ID NO:933, SEQ ID NO:934, SEQ ID NO:935, SEQ ID NO:936, SEQ ID NO:937, SEQ ID NO:938, SEQ ID NO:939, SEQ ID NO:940, SEQ ID NO:941, SEQ ID NO:942, SEQ ID NO:943, SEQ ID NO:944, SEQ ID NO:945, SEQ ID NO:946, SEQ ID NO:947, SEQ ID NO:948, SEQ ID NO:949, SEQ ID NO:950, SEQ ID NO:951, SEQ ID NO:952, SEQ ID NO:953, SEQ ID NO:954, SEQ ID NO:955, SEQ ID NO:956, SEQ ID NO:957, SEQ ID NO:958, SEQ ID NO:959, SEQ ID NO:960, SEQ ID NO:961, SEQ ID NO:962, SEQ ID NO:963, SEQ ID NO:964, SEQ ID NO:965, SEQ ID NO:966, SEQ ID NO:967, SEQ ID NO:968, SEQ ID NO:969, SEQ ID NO:970, SEQ ID NO:971, SEQ ID NO:972, SEQ ID NO:973, SEQ ID NO:974, SEQ ID NO:975, SEQ ID NO:976, SEQ ID NO:977, SEQ ID NO:978, SEQ ID NO:979, SEQ ID NO:980, SEQ ID NO:981, SEQ ID NO:982, SEQ ID NO:983, SEQ ID NO:984, SEQ ID NO:985, SEQ ID NO:986, SEQ ID NO:987, SEQ ID NO:988, SEQ ID NO:989, SEQ ID NO:990, SEQ ID NO:991, SEQ ID NO:992, SEQ ID NO:993, SEQ ID NO:994, SEQ ID NO:995, SEQ ID NO:996, SEQ ID NO:997, SEQ ID NO:998, SEQ ID NO:999, SEQ ID NO:1000, SEQ ID NO:1001, SEQ ID NO:1002, SEQ ID NO:1003, SEQ ID NO:1004, SEQ ID NO:1005, SEQ ID NO:1006, SEQ ID NO:1007, SEQ ID NO:1008, SEQ ID NO:1009, SEQ ID NO:1010, SEQ ID NO:1011, SEQ ID NO:1012, SEQ ID NO:1013, SEQ ID NO:1014, SEQ ID NO:1015,

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NO:1317, SEQ ID NO:1318, SEQ ID NO:1319, SEQ ID NO:1320, SEQ ID NO:1321, SEQ ID NO:1322, SEQ ID NO:1323, SEQ ID NO:1324, SEQ ID NO:1325, SEQ ID NO:1326, SEQ ID NO:1327, SEQ ID NO:1328, SEQ ID NO:1329, SEQ ID NO:1330, SEQ ID NO:1331, SEQ ID NO:1332, SEQ ID NO:1333, SEQ ID NO:1334, SEQ ID NO:1335, SEQ ID NO:1336, SEQ ID NO:1337, SEQ ID NO:1338, SEQ ID NO:1339, SEQ ID NO:1340, SEQ ID NO:1341, SEQ ID NO:1342, SEQ ID NO:1343, SEQ ID NO:1344, SEQ ID NO:1345, SEQ ID NO:1346, SEQ ID NO:1347, SEQ ID NO:1348, SEQ ID NO:1349, SEQ ID NO:1350, SEQ ID NO:1351, SEQ ID NO:1352, SEQ ID NO:1353, SEQ ID NO:1354, SEQ ID NO:1355, SEQ ID NO:1356, SEQ ID NO:1357, SEQ ID NO:1358, SEQ ID NO:1359, SEQ ID NO:1360, SEQ ID NO:1361, SEQ ID NO:1362, SEQ ID NO:1363, SEQ ID NO:1364, SEQ ID NO:1365, SEQ ID NO:1366, SEQ ID NO:1367, SEQ ID NO:1368, SEQ ID NO:1369, SEQ ID NO:1370, SEQ ID NO:1371, SEQ ID NO:1372, SEQ ID NO:1373, SEQ ID NO:1374, SEQ ID NO:1375, SEQ ID NO:1376, SEQ ID NO:1377, SEQ ID NO:1378, SEQ ID NO:1379, and SEQ ID NO:1380.

28. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1381, SEQ ID NO:1382, SEQ ID NO:1383, SEQ ID NO:1384, SEQ ID NO:1385, SEQ ID NO:1386, SEQ ID NO:1387, SEQ ID NO:1388, SEQ ID NO:1389, SEQ ID NO:1390, SEQ ID NO:1391, SEQ ID NO:1392, SEQ ID NO:1393, SEQ ID NO:1394, SEQ ID NO:1395, SEQ ID NO:1396, SEQ ID NO:1397, SEQ ID NO:1398, SEQ ID NO:1399, SEQ ID NO:1400, SEQ ID NO:1401, SEQ ID NO:1402, SEQ ID NO:1403, SEQ ID NO:1404, SEQ ID NO:1405, SEQ ID NO:1406, SEQ ID NO:1407, SEQ ID NO:1408, SEQ ID NO:1409, SEQ ID NO:1410, SEQ ID NO:1411, SEQ ID NO:1412, SEQ ID NO:1413, SEQ ID NO:1414, SEQ ID NO:1415, SEQ ID NO:1416, SEQ ID NO:1417, SEQ ID NO:1418, SEQ ID NO:1419, SEQ ID NO:1420, SEQ ID NO:1421, SEQ ID NO:1422, SEQ ID NO:1423, SEQ ID NO:1424, SEQ ID NO:1425, SEQ ID NO:1426, SEQ ID NO:1427, SEQ ID NO:1428, SEQ ID NO:1429, SEQ ID NO:1430, SEQ ID NO:1431, SEQ ID NO:1432, SEQ ID NO:1433, SEQ ID NO:1434, SEQ ID NO:1435, SEQ ID NO:1436, SEQ ID NO:1437, SEQ ID NO:1438, SEQ ID NO:1439, SEQ ID NO:1440, SEQ ID NO:1441, SEQ ID NO:1442, SEQ ID NO:1443, SEQ ID NO:1444, SEQ ID NO:1445, SEQ ID NO:1446, SEQ ID NO:1447, SEQ ID NO:1448, SEQ ID NO:1449, SEQ ID NO:1450, SEQ ID NO:1451, SEQ ID NO:1452, SEQ ID NO:1453, SEQ ID NO:1454, SEQ ID NO:1455, SEQ ID NO:1456, SEQ ID NO:1457, SEQ ID NO:1458, SEQ ID NO:1459, SEQ ID NO:1460, SEQ ID NO:1461, SEQ ID NO:1462, SEQ ID NO:1463, SEQ ID NO:1464, SEQ ID NO:1465, SEQ ID NO:1466, SEQ ID NO:1467, SEQ ID NO:1468, SEQ ID NO:1469, SEQ ID NO:1470, SEQ ID NO:1471, SEQ ID NO:1472, SEQ ID NO:1473, SEQ ID NO:1474, SEQ ID NO:1475, SEQ ID NO:1476, SEQ ID NO:1477, SEQ ID NO:1478, SEQ ID NO:1479, SEQ ID NO:1480, SEQ ID NO:1481, SEQ ID NO:1482, SEQ ID NO:1483, SEQ ID NO:1484, SEQ ID NO:1485, SEQ ID NO:1486, SEQ ID NO:1487, SEQ ID NO:1488, SEQ ID NO:1489, SEQ ID NO:1490, SEQ ID NO:1491, SEQ ID NO:1492, SEQ ID NO:1493, SEQ ID NO:1494, SEQ ID NO:1495, SEQ ID NO:1496, SEQ ID NO:1497, SEQ ID NO:1498, SEQ ID NO:1499, SEQ ID NO:1500, SEQ ID NO:1501, SEQ ID NO:1502, SEQ ID NO:1503, SEQ ID NO:1504, SEQ ID NO:1505, SEQ ID NO:1506, SEQ ID NO:1507, SEQ ID NO:1508, SEQ ID NO:1509, SEQ ID NO:1510, SEQ ID NO:1511, SEQ ID NO:1512, SEQ ID NO:1513, SEQ ID NO:1514, SEQ ID NO:1515, SEQ ID NO:1516, SEQ ID NO:1517, SEQ ID NO:1518, SEQ ID NO:1519, SEQ ID NO:1520, SEQ ID NO:1521, SEQ ID NO:1522, SEQ ID NO:1523, SEQ ID NO:1524, SEQ ID NO:1525, SEQ ID NO:1526, SEQ ID NO:1527, SEQ ID NO:1528, SEQ ID NO:1529, SEQ ID NO:1530, SEQ ID NO:1531, SEQ ID NO:1532, SEQ ID NO:1533, SEQ ID NO:1534, SEQ ID NO:1535, SEQ ID NO:1536, SEQ ID NO:1537, SEQ ID NO: NO:1538, SEQ ID NO:1539, SEQ ID NO:1540, SEQ ID NO:1541, SEQ ID NO:1542, SEQ ID NO:1543, SEQ ID NO:1544, SEQ ID NO:1545, SEQ ID NO:1546, SEQ ID NO:1547, SEQ ID NO:1548, SEQ ID NO:1549, SEQ ID NO:1550, SEQ ID NO:1551, SEQ ID NO:1552, SEQ ID NO:1553, SEQ ID NO:1554, SEQ ID NO:1555, SEQ ID NO:1556, SEQ ID NO:1557, SEQ ID NO:1558, SEQ ID NO:1559, SEQ ID NO:1560, SEQ ID NO:1561, SEQ ID NO:1562, SEQ ID NO:1563, SEQ ID NO:1564, SEQ ID NO:1565, SEQ ID NO:1566, SEQ ID NO:1567, SEQ ID NO:1568, SEQ ID NO:1569, SEQ ID NO:1570, SEQ ID NO:1571, SEQ ID NO:1572, SEQ ID NO:1573, SEQ ID NO:1574, SEQ ID NO:1575, SEQ ID NO:1576, SEQ ID NO:1577, SEQ ID NO:1578, SEQ ID NO:1579, SEQ ID NO:1580, SEQ ID NO:1581, SEQ ID NO:1582, SEQ ID NO:1583, SEQ ID NO:1584, SEQ ID NO:1585, SEQ ID NO:1586, SEQ ID NO:1587, SEQ ID NO:1588, SEQ ID

NO:1593, SEQ ID NO:1594, SEQ ID NO:1595, SEQ ID NO:1596, SEQ ID NO:1597, SEQ ID NO:1598, SEQ ID NO:1599, SEQ ID NO:1600, SEQ ID NO:1601, SEQ ID NO:1602, SEQ ID NO:1603, SEQ ID NO:1604, SEQ ID NO:1605, SEQ ID NO:1606, SEQ ID NO:1607, SEQ ID NO:1608, SEQ ID NO:1609, SEQ ID NO:1610, SEQ ID NO:1611, SEQ ID NO:1612, SEQ ID NO:1613, SEQ ID NO:1614, SEQ ID NO:1615, SEQ ID NO:1616, SEQ ID NO:1617, SEQ ID NO:1618, SEQ ID NO:1619, SEQ ID NO:1620, SEQ ID NO:1621, SEQ ID NO:1622, SEQ ID NO:1623, SEQ ID NO:1624, SEQ ID NO:1625, SEQ ID NO:1626, SEQ ID NO:1627, SEQ ID NO:1628, SEQ ID NO:1629, SEQ ID NO:1630, SEQ ID NO:1631, SEQ ID NO:1632, SEQ ID NO:1633, SEQ ID NO:1634, SEQ ID NO:1635, SEQ ID NO:1636, SEQ ID NO:1637, SEQ ID NO:1638, SEQ ID NO:1639, SEQ ID NO:1640, SEQ ID NO:1641, SEQ ID NO:1642, SEQ ID NO:1643, SEQ ID NO:1644, SEQ ID NO:1645, SEQ ID NO:1646, SEQ ID NO:1647, SEQ ID NO:1648, SEQ ID NO:1649, SEQ ID NO:1650, SEQ ID NO:1651, SEQ ID NO:1652, SEQ ID NO:1653, SEQ ID NO:1654, SEQ ID NO:1655, SEQ ID NO:1656, SEQ ID NO:1657, SEQ ID NO:1658, SEQ ID NO:1659, SEQ ID NO:1660, SEQ ID NO:1661, SEQ ID NO:1662, SEQ ID NO:1663, SEQ ID NO:1664, SEQ ID NO:1665, SEQ ID NO:1666, SEQ ID NO:1667, SEQ ID NO:1668, SEQ ID NO:1669, SEQ ID NO:1670, SEQ ID NO:1671, SEQ ID NO:1672, SEQ ID NO:1673, SEQ ID NO:1674, SEQ ID NO:1675, SEQ ID NO:1676, SEQ ID NO:1677, SEQ ID NO:1678, SEQ ID NO:1679, SEQ ID NO:1680, SEQ ID NO:1681, SEQ ID NO:1682, SEQ ID NO:1683, SEQ ID NO:1684, SEQ ID NO:1685, SEQ ID NO:1686, SEQ ID NO:1687, SEQ ID NO:1688, SEQ ID NO:1689, SEQ ID NO:1690, SEQ ID NO:1691, SEQ ID NO:1692, SEQ ID NO:1693, SEQ ID NO:1694, SEQ ID NO:1695, SEQ ID NO:1696, SEQ ID NO:1697, SEQ ID NO:1698, SEQ ID NO:1699, SEQ ID NO:1700, SEQ ID NO:1701, SEQ ID NO:1702, SEQ ID NO:1703, SEQ ID NO:1704, SEQ ID NO:1705, SEQ ID NO:1706, SEQ ID NO:1707, SEQ ID NO:1708, SEQ ID NO:1709, SEQ ID NO:1710, SEQ ID NO:1711, SEQ ID NO:1712, SEQ ID NO:1713, SEQ ID NO:1714, SEQ ID NO:1715, SEQ ID NO:1716, SEQ ID NO:1717, SEQ ID NO:1718, SEQ ID NO:1719, SEQ ID NO:1720, SEQ ID NO:1721, SEQ ID NO:1722, SEQ ID NO:1723, SEQ ID NO:1724, SEQ ID NO:1725, SEQ ID NO:1726, SEQ ID NO:1727, SEQ ID NO:1728, SEQ ID NO:1729, SEQ ID NO:1730, SEQ ID NO:1731, SEQ ID NO:1732, SEQ ID NO:1733, SEQ ID NO:1734, SEQ ID NO:1735, SEQ ID NO:1736, SEQ ID NO:1737, SEQ ID NO:1738, SEQ ID NO:1739, SEQ ID NO:1740, SEQ ID NO:1741, SEQ ID NO:1742, SEQ ID NO:1743, SEQ ID NO:1744, SEQ ID NO:1745, SEQ ID NO:1746, SEQ ID NO:1747, SEQ ID NO:1748, SEQ ID NO:1749, SEQ ID NO:1750, SEQ ID NO:1751, SEQ ID NO:1752, SEQ ID NO:1753, SEQ ID NO:1754, SEQ ID NO:1755, SEQ ID NO:1756, SEQ ID NO:1757, SEQ ID NO:1758, SEQ ID NO:1759, SEQ ID NO:1760, SEQ ID NO:1761, SEQ ID NO:1762, SEQ ID NO:1763, SEQ ID NO:1764, SEQ ID NO:1765, SEQ ID NO:1766, SEQ ID NO:1767, SEQ ID NO:1768, SEQ ID NO:1769, SEQ ID NO:1770, SEQ ID NO:1771, SEQ ID NO:1772, SEQ ID NO:1773, SEQ ID NO:1774, SEQ ID NO:1775, SEQ ID NO:1776, SEQ ID NO:1777, SEQ ID NO:1778, SEQ ID NO:1779, SEQ ID NO:1780, SEQ ID NO:1781, SEQ ID NO:1782, SEQ ID NO:1783, SEQ ID NO:1784, SEQ ID NO:1785, SEQ ID NO:1786, SEQ ID NO:1787, SEQ ID NO:1788, SEQ ID NO:1789, SEQ ID NO:1790, SEQ ID NO:1791, SEQ ID NO:1792, SEQ ID NO:1793, SEQ ID NO:1794, SEQ ID NO:1795, SEQ ID NO:1796, SEQ ID NO:1797, SEQ ID NO:1798, SEQ ID NO:1799, SEQ ID NO:1800, SEQ ID NO:1801, SEQ ID NO:1802, SEQ ID NO:1803, SEQ ID NO:1804, SEQ ID NO:1805, SEQ ID NO:1806, SEQ ID NO:1807, SEQ ID NO:1808, SEQ ID NO:1809, SEQ ID NO:1810, SEQ ID NO:1811, SEQ ID NO:1812, SEQ ID NO:1813, SEQ ID NO:1814, SEQ ID NO:1815, SEQ ID NO:1816, SEQ ID NO:1817, SEQ ID NO:1818, SEQ ID NO:1819, SEQ ID NO:1820, SEQ ID NO:1821, SEQ ID NO:1822, SEQ ID NO:1823, SEQ ID NO:1824, SEQ ID NO:1825, SEQ ID NO:1826, SEQ ID NO:1827, SEQ ID NO:1828, SEQ ID NO:1829, SEQ ID NO:1830, SEQ ID NO:1831, SEQ ID NO:1832, SEQ ID NO:1833, SEQ ID NO:1834, SEQ ID NO:1835, SEQ ID NO:1836, SEQ ID NO:1837, SEQ ID NO:1838, SEQ ID NO:1839, SEQ ID NO:1840, SEQ ID NO:1841, SEQ ID NO:1842, SEQ ID NO:1843, SEQ ID NO:1844, SEQ ID NO:1845, SEQ ID NO:1846, SEQ ID NO:1847, SEQ ID NO:1848, SEQ ID NO:1849, SEQ ID NO:1850, SEQ ID NO:1851, SEQ ID NO:1852, SEQ ID NO:1853, SEQ ID NO:1854, SEQ ID NO:1855, SEQ ID NO:1856, SEQ ID NO:1857, SEQ ID NO:1858, and SEQ ID NO:1859.

29. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1860, SEQ ID NO:1861, SEQ ID NO:1862, SEQ ID NO:1863, SEQ ID NO:1864, SEQ ID NO:1865, SEQ ID

SEQ ID NO:1871, SEQ ID NO:1872, SEQ ID NO:1873, SEQ ID NO:1874, SEQ ID NO:1875, SEQ ID NO:1876, SEQ ID NO:1877, SEQ ID NO:1878, SEQ ID NO:1879, SEQ ID NO:1880, SEQ ID NO:1881, SEQ ID NO:1882, SEQ ID NO:1883, SEQ ID NO:1884, SEQ ID NO:1885, SEQ ID NO:1886, SEQ ID NO:1887, SEQ ID NO:1888, SEQ ID NO:1889, SEQ ID NO:1890, SEQ ID NO:1891, SEQ ID NO:1892, SEQ ID NO:1893, SEQ ID NO:1894, SEQ ID NO:1895, SEQ ID NO:1896, SEQ ID NO:1897, SEQ ID NO:1898, SEQ ID NO:1899, SEQ ID NO:1900, SEQ ID NO:1901, SEQ ID NO:1902, SEQ ID NO:1903, SEQ ID NO:1904, SEQ ID NO:1905, SEQ ID NO:1906, SEQ ID NO:1907, SEQ ID NO:1908, SEQ ID NO:1909, SEQ ID NO:1910, SEQ ID NO:1911, SEQ ID NO:1912, SEQ ID NO:1913, SEQ ID NO:1914, SEQ ID NO:1915, SEQ ID NO:1916, SEQ ID NO:1917, SEQ ID NO:1918, SEQ ID NO:1919, SEQ ID NO:1920, SEQ ID NO:1921, SEQ ID NO:1922, SEQ ID NO:1923, SEQ ID NO:1924, SEQ ID NO:1925, SEQ ID NO:1926, SEQ ID NO:1927, SEQ ID NO:1928, SEQ ID NO:1929, SEQ ID NO:1930, SEQ ID NO:1931, SEQ ID NO:1932, SEQ ID NO:1933, SEQ ID NO:1934, SEQ ID NO:1935, SEQ ID NO:1936, SEQ ID NO:1937, SEQ ID NO:1938, SEQ ID NO:1939, SEQ ID NO:1940, SEQ ID NO:1941, SEQ ID NO:1942, SEQ ID NO:1943, SEQ ID NO:1944, SEQ ID NO:1945, SEQ ID NO:1946, SEQ ID NO:1947, SEQ ID NO:1948, SEQ ID NO:1949, SEQ ID NO:1950, SEQ ID NO:1951, SEQ ID NO:1952, SEQ ID NO:1953, SEQ ID NO:1954, SEQ ID NO:1955, SEQ ID NO:1956, SEQ ID NO:1957, SEQ ID NO:1958, SEQ ID NO:1959, SEQ ID NO:1960, SEQ ID NO:1961, SEQ ID NO:1962, SEQ ID NO:1963, SEQ ID NO:1964, SEQ ID NO:1965, SEQ ID NO:1966, SEQ ID NO:1967, SEQ ID NO:1968, SEQ ID NO:1969, SEQ ID NO:1970, SEQ ID NO:1971, SEQ ID NO:1972, SEQ ID NO:1973, SEQ ID NO:1974, SEQ ID NO:1975, SEQ ID NO:1976, SEQ ID NO:1977, SEQ ID NO:1978, SEQ ID NO:1979, SEQ ID NO:1980, SEQ ID NO:1981, SEQ ID NO:1982, SEQ ID NO:1983, SEQ ID NO:1984, SEQ ID NO:1985, SEQ ID NO:1986, SEQ ID NO:1987, SEQ ID NO:1988, SEQ ID NO:1989, SEQ ID NO:1990, SEQ ID NO:1991, SEQ ID NO:1992, SEQ ID NO:1993, SEQ ID NO:1994, SEQ ID NO:1995, SEQ ID NO:1996, SEQ ID NO:1997, SEQ ID NO:1998, SEQ ID NO:1999, SEQ ID NO:2000, SEQ ID NO:2001, SEQ ID NO:2002, SEQ ID NO:2003, SEQ ID NO:2004, SEQ ID NO:2005, SEQ ID NO:2006, SEQ ID NO:2007, SEQ ID NO:2008, SEQ ID NO:2009, SEQ ID NO:2010, SEQ ID NO:2011, SEQ ID NO:2012, SEQ ID NO:2013, SEQ ID NO:2014, SEQ ID NO:2015, SEQ ID NO:2016, SEQ ID NO:2017, SEQ ID NO:2018, SEQ ID NO:2019, SEQ ID NO:2020, SEQ ID NO:2021, SEQ ID NO:2022, SEQ ID NO:2023, SEQ ID NO:2024, SEQ ID NO:2025, SEQ ID NO:2026, SEQ ID NO:2027, SEQ ID NO:2028, SEQ ID NO:2029, SEQ ID NO:2030, SEQ ID NO:2031, SEQ ID NO:2032, SEQ ID NO:2033, SEQ ID NO:2034, SEQ ID NO:2035, SEQ ID NO:2036, SEQ ID NO:2037, SEQ ID NO:2038, SEQ ID NO:2039, SEQ ID NO:2040, SEQ ID NO:2041, SEQ ID NO:2042, SEQ ID NO:2043, SEQ ID NO:2044, SEQ ID NO:2045, SEQ ID NO:2046, SEQ ID NO:2047, SEQ ID NO:2048, SEQ ID NO:2049, SEQ ID NO:2050, SEQ ID NO:2051, SEQ ID NO:2052, SEQ ID NO:2053, SEQ ID NO:2054, SEQ ID NO:2055, SEQ ID NO:2056, SEQ ID NO:2057, SEQ ID NO:2058, SEQ ID NO:2059, SEQ ID NO:2060, SEQ ID NO:2061, SEQ ID NO:2062, SEQ ID NO:2063, SEQ ID NO:2064, SEQ ID NO:2065, SEQ ID NO:2066, SEQ ID NO:2067, SEQ ID NO:2068, SEQ ID NO:2069, SEQ ID NO:2070, SEQ ID NO:2071, SEQ ID NO:2072, SEQ ID NO:2073, SEQ ID NO:2074, SEQ ID NO:2075, SEQ ID NO:2076, SEQ ID NO:2077, SEQ ID NO:2078, SEQ ID NO:2079, SEQ ID NO:2080, SEQ ID NO:2081, SEQ ID NO:2082, SEQ ID NO:2083, SEQ ID NO:2084, SEQ ID NO:2085, SEQ ID NO:2086, SEQ ID NO:2087, SEQ ID NO:2088, SEQ ID NO:2089, SEQ ID NO:2090, SEQ ID NO:2091, SEQ ID NO:2092, SEQ ID NO:2093, SEQ ID NO:2094, SEQ ID NO:2095, SEQ ID NO:2096, SEQ ID NO:2097, SEQ ID NO:2098, SEQ ID NO:2099, SEQ ID NO:2100, SEQ ID NO:2101, SEQ ID NO:2102, SEQ ID NO:2103, SEQ ID NO:2104, and SEQ ID NO:2105.

30. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence selected from the group consisting of SEQ SEQ ID NO:2106, SEQ ID NO:2107, SEQ ID NO:2108, SEQ ID NO:2109, SEQ ID NO:2110, SEQ ID NO:2111, SEQ ID NO:2112, SEQ ID NO:2113, SEQ ID NO:2114, SEQ ID NO:2115, SEQ ID NO:2116, SEQ ID NO:2117, SEQ ID NO:2118, SEQ ID NO:2119, SEQ ID NO:2120, SEQ ID NO:2121, SEQ ID NO:2122, SEQ ID NO:2123, SEQ ID NO:2124, SEQ ID NO:2125, SEQ ID NO:2126, SEQ ID NO:2127, SEQ ID NO:2128, SEQ ID NO:2129, SEQ ID NO:2130, SEQ ID NO:2131, SEQ ID NO:2132, SEQ ID NO:2133, SEQ ID NO:2134, SEQ ID NO:2135, SEQ ID NO:2136, SEQ ID NO:2137, SEQ ID NO:2138, SEQ ID NO:2139, SEQ ID NO:2140, SEQ ID NO:2141, SEQ ID NO:2142, SEQ ID

NO:2145, SEQ ID NO:2146, SEQ ID NO:2147, SEQ ID NO:2148, SEQ ID NO:2149, SEQ ID NO:2150, SEQ ID NO:2151, SEQ ID NO:2152, SEQ ID NO:2153, SEQ ID NO:2154, SEQ ID NO:2155, SEQ ID NO:2156, SEQ ID NO:2157, SEQ ID NO:2158, SEQ ID NO:2159, SEQ ID NO:2160, SEQ ID NO:2161, SEQ ID NO:2162, SEQ ID NO:2163, SEQ ID NO:2164, SEQ ID NO:2165, SEQ ID NO:2166, SEQ ID NO:2167, SEQ ID NO:2168, SEQ ID NO:2169, SEQ ID NO:2170, SEQ ID NO:2171, SEQ ID NO:2172, SEQ ID NO:2173, SEQ ID NO:2174, SEQ ID NO:2175, SEQ ID NO:2176, SEQ ID NO:2177, SEQ ID NO:2178, SEQ ID NO:2179, SEQ ID NO:2180, SEQ ID NO:2181, SEQ ID NO:2182, SEQ ID NO:2183, SEQ ID NO:2184, SEQ ID NO:2185, SEQ ID NO:2186, SEQ ID NO:2187, SEQ ID NO:2188, SEQ ID NO:2189, SEQ ID NO:2190, SEQ ID NO:2191, SEQ ID NO:2192, SEQ ID NO:2193, SEQ ID NO:2194, SEQ ID NO:2195, SEQ ID NO:2196, SEQ ID NO:2197, SEQ ID NO:2198, SEQ ID NO:2199, SEQ ID NO:2200, SEQ ID NO:2201, SEQ ID NO:2202, SEQ ID NO:2203, SEQ ID NO:2204, SEQ ID NO:2205, SEQ ID NO:2206, SEQ ID NO:2207, SEQ ID NO:2208, SEQ ID NO:2209, SEQ ID NO:2210, SEQ ID NO:2211, SEQ ID NO:2212, SEQ ID NO:2213, SEQ ID NO:2214, SEQ ID NO:2215, SEQ ID NO:2216, SEQ ID NO:2217, SEQ ID NO:2218, SEQ ID NO:2219, SEQ ID NO:2220, SEQ ID NO:2221, SEQ ID NO:2222, SEQ ID NO:2223, SEQ ID NO:2224, SEQ ID NO:2225, SEQ ID NO:2226, SEQ ID NO:2227, SEQ ID NO:2228, SEQ ID NO:2229, SEQ ID NO:2230, SEQ ID NO:2231, SEQ ID NO:2232, SEQ ID NO:2233, SEQ ID NO:2234, SEQ ID NO:2235, SEQ ID NO:2236, SEQ ID NO:2237, SEQ ID NO:2238, SEQ ID NO:2239, SEQ ID NO:2240, SEQ ID NO:2241, SEQ ID NO:2242, SEQ ID NO:2243, SEQ ID NO:2244, SEQ ID NO:2245, SEQ ID NO:2246, SEQ ID NO:2247, SEQ ID NO:2248, SEQ ID NO:2249, SEQ ID NO:2250, SEQ ID NO:2251, SEQ ID NO:2252, SEQ ID NO:2253, SEQ ID NO:2254, SEQ ID NO:2255, SEQ ID NO:2256, SEQ ID NO:2257, SEQ ID NO:2258, SEQ ID NO:2259, SEQ ID NO:2260, SEQ ID NO:2261, SEQ ID NO:2262, SEQ ID NO:2263, SEQ ID NO:2264, SEQ ID NO:2265, SEQ ID NO:2266, SEQ ID NO:2267, SEQ ID NO:2268, SEQ ID NO:2269, SEQ ID NO:2270, SEQ ID NO:2271, SEQ ID NO:2272, SEQ ID NO:2273, SEQ ID NO:2274, SEQ ID NO:2275, SEQ ID NO:2276, SEQ ID NO:2277, SEQ ID NO:2278, SEQ ID NO:2279, SEQ ID NO:2280, SEQ ID NO:2281, SEQ ID NO:2282, SEQ ID NO:2283, SEQ ID NO:2284, SEQ ID NO:2285, SEQ ID NO:2286, SEQ ID NO:2287, SEQ ID NO:2288, SEQ ID NO:2289, SEQ ID NO:2290, SEQ ID NO:2291, SEQ ID NO:2292, SEQ ID NO:2293, SEQ ID NO:2294, SEQ ID NO:2295, SEQ ID NO:2296, SEQ ID NO:2297, SEQ ID NO:2298, SEQ ID NO:2299, SEQ ID NO:2300, SEQ ID NO:2301, SEQ ID NO:2302, SEQ ID NO:2303, SEQ ID NO:2304, SEQ ID NO:2305, SEQ ID NO:2306, SEQ ID NO:2307, SEQ ID NO:2308, SEQ ID NO:2309, SEQ ID NO:2310, SEQ ID NO:2311, SEQ ID NO:2312, SEQ ID NO:2313, SEQ ID NO:2314, SEQ ID NO:2315, SEQ ID NO:2316, SEQ ID NO:2317, SEQ ID NO:2318, SEQ ID NO:2319, SEQ ID NO:2320, SEQ ID NO:2321, SEQ ID NO:2322, SEQ ID NO:2323, SEQ ID NO:2324, SEQ ID NO:2325, SEQ ID NO:2326, SEQ ID NO:2327, SEQ ID NO:2328, SEQ ID NO:2329, SEQ ID NO:2330, SEQ ID NO:2331, SEQ ID NO:2332, SEQ ID NO:2333, SEQ ID NO:2334, SEQ ID NO:2335, SEQ ID NO:2336, SEQ ID NO:2337, SEQ ID NO:2338, SEQ ID NO:2339, SEQ ID NO:2340, SEQ ID NO:2341, SEQ ID NO:2342, SEQ ID NO:2343, SEQ ID NO:2344, SEQ ID NO:2345, SEQ ID NO:2346, SEQ ID NO:2347, SEQ ID NO:2348, SEQ ID NO:2349, SEQ ID NO:2350, SEQ ID NO:2351, SEQ ID NO:2352, SEQ ID NO:2353, SEQ ID NO:2354, SEQ ID NO:2355, SEQ ID NO:2356, SEQ ID NO:2357, SEQ ID NO:2358, SEQ ID NO:2359, SEQ ID NO:2360, SEQ ID NO:2361, SEQ ID NO:2362, SEQ ID NO:2363, SEQ ID NO:2364, SEQ ID NO:2365, SEQ ID NO:2366, SEQ ID NO:2367, SEQ ID NO:2368, SEQ ID NO:2369, SEQ ID NO:2370, SEQ ID NO:2371, SEQ ID NO:2372, SEQ ID NO:2373, SEQ ID NO:2374, and SEQ ID NO:2375.

31. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first isolated coding region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:2376, SEQ ID NO:2377, SEQ ID NO:2378, SEQ ID NO:2379, SEQ ID NO:2380, SEQ ID NO:2381, SEQ ID NO:2382, SEQ ID NO:2383, SEQ ID NO:2384, SEQ ID NO:2385, SEQ ID NO:2386, SEQ ID NO:2387, SEQ ID NO:2388, SEQ ID NO:2389, SEQ ID NO:2390, SEQ ID NO:2391, SEQ ID NO:2392, SEQ ID NO:2393, SEQ ID NO:2394, SEQ ID NO:2395, SEQ ID NO:2396, SEQ ID NO:2397, SEQ ID NO:2398, SEQ ID NO:2399, SEQ ID NO:2400, SEQ ID NO:2401, SEQ ID NO:2402, SEQ ID NO:2403, SEQ ID NO:2404, SEQ ID NO:2405, SEQ ID NO:2406, SEQ ID NO:2407, SEQ ID NO:2408, SEQ ID NO:2409, SEQ ID NO:2410, SEQ ID NO:2411, SEQ ID NO:2412, SEQ ID NO:2413, SEQ ID NO:2414, SEQ ID NO:2415, SEQ ID NO:2416, SEQ ID NO:2417, SEQ ID NO:2418, SEQ ID NO:2419, SEQ ID NO:2420, SEQ ID NO:2421, SEQ ID NO:2422,

NO:2427, SEQ ID NO:2428, SEQ ID NO:2429, SEQ ID NO:2430, SEQ ID NO:2431, SEQ ID NO:2432, SEQ ID NO:2433, SEQ ID NO:2434, SEQ ID NO:2435, SEQ ID NO:2436, SEQ ID NO:2437, SEQ ID NO:2438, SEQ ID NO:2439, SEQ ID NO:2440, SEQ ID NO:2441, SEQ ID NO:2442, SEQ ID NO:2443, SEQ ID NO:2444, SEQ ID NO:2445, SEQ ID NO:2446, SEQ ID NO:2447, SEQ ID NO:2448, SEQ ID NO:2449, SEQ ID NO:2450, SEQ ID NO:2451, SEQ ID NO:2452, SEQ ID NO:2453, SEQ ID NO:2454, SEQ ID NO:2455, SEQ ID NO:2456, SEQ ID NO:2457, SEQ ID NO:2458, SEQ ID NO:2459, SEQ ID NO:2460, SEQ ID NO:2461, SEQ ID NO:2462, SEQ ID NO:2463, SEQ ID NO:2464, SEQ ID NO:2465, SEQ ID NO:2466, SEQ ID NO:2467, SEQ ID NO:2468, SEQ ID NO:2469, SEQ ID NO:2470, SEQ ID NO:2471, SEQ ID NO:2472, SEQ ID NO:2473, SEQ ID NO:2474, SEQ ID NO:2475, SEQ ID NO:2476, SEQ ID NO:2477, SEQ ID NO:2478, SEQ ID NO:2479, SEQ ID NO:2480, SEQ ID NO:2481, SEQ ID NO:2482, SEQ ID NO:2483, SEQ ID NO:2484, SEQ ID NO:2485, SEQ ID NO:2486, SEQ ID NO:2487, SEQ ID NO:2488, SEQ ID NO:2489, SEQ ID NO:2490, SEQ ID NO:2491, SEQ ID NO:2492, SEQ ID NO:2493, SEQ ID NO:2494, SEQ ID NO:2495, SEQ ID NO:2496, SEQ ID NO:2497, SEQ ID NO:2498, SEQ ID NO:2499, SEQ ID NO:2500, SEQ ID NO:2501, SEQ ID NO:2502, SEQ ID NO:2503, SEQ ID NO:2504, SEQ ID NO:2505, SEQ ID NO:2506, SEQ ID NO:2507, SEQ ID NO:2508, SEQ ID NO:2509, SEQ ID NO:2510, SEQ ID NO:2511, SEQ ID NO:2512, SEQ ID NO:2513, SEQ ID NO:2514, SEQ ID NO:2515, SEQ ID NO:2516, SEQ ID NO:2517, SEQ ID NO:2518 SEQ ID NO:2519, SEQ ID NO:2520, SEQ ID NO:2521, SEQ ID NO:2522, SEQ ID NO:2523, SEQ ID NO:2524, SEQ ID NO:2525, SEQ ID NO:2526, SEQ ID NO:2527, SEQ ID NO:2528, SEQ ID NO:2529, SEQ ID NO:2530, SEQ ID NO:2531, and SEQ ID NO:2532.

32. The isolated **peptide** or **polypeptide** of claim 1, wherein said amino acid sequence consists essentially of the sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

33. The isolated **peptide** or **polypeptide** of claim 32, wherein said amino acid sequence consists of the sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

34. The isolated **peptide** or **polypeptide** of claim 1, wherein said at least a first coding region comprises an amino acid sequence that is encoded by an at least 100 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

35. The isolated **peptide** or **polypeptide** of claim 34, wherein said at least a first coding region comprises an amino acid sequence that is encoded by an at least 200 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

36. The isolated **peptide** or **polypeptide** of claim 35, wherein said at least a first coding region comprises an amino acid sequence that is encoded by a nucleic acid segment comprising the nucleotide sequence of any one of SEQ ID NO:1 to SEQ ID NO:668.

37. The isolated **peptide** or **polypeptide** of claim 36, wherein said at least a first coding region comprises an amino acid sequence that is encoded by a nucleic acid segment that consists essentially of the nucleotide sequence of any one of SEQ ID NO:1 to SEQ ID NO:668.

38. The isolated **peptide** or **polypeptide** of claim 37, wherein said at least a first coding region comprises an amino acid sequence that is encoded by a nucleic acid segment that consists of the nucleotide sequence of any one of SEQ ID NO:1 to SEQ ID NO:668.

39. A composition comprising the isolated **peptide** or **polypeptide** of claim 1.

40. The composition according to claim 39, further comprising a pharmaceutically-acceptable diluent.

41. An isolated polynucleotide, comprising at least a first nucleic acid

segment that (a) encodes the isolated **peptide** or **polypeptide** of claim 1; or (b) comprises an at least 100 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

42. The isolated polynucleotide of claim 41, comprising at least a first nucleic acid segment that encodes the isolated **peptide** or **polypeptide** of claim 1.

43. The isolated polynucleotide of claim 41, comprising at least a first nucleic acid segment that comprises an at least 25 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

44. The isolated polynucleotide of claim 43, comprising at least a first nucleic acid segment that comprises an at least 50 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

45. The isolated polynucleotide of claim 44, comprising at least a first nucleic acid segment that comprises an at least 75 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

46. The isolated polynucleotide of claim 45, comprising at least a first nucleic acid segment that comprises an at least 100 contiguous nucleotide sequence from any one of SEQ ID NO:1 to SEQ ID NO:668.

47. The isolated polynucleotide of claim 46, wherein said at least a first nucleic acid segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110 , SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192 SEQ

SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, and SEQ ID NO:278.

48. The isolated polynucleotide of claim 46, wherein said at least a first nucleic acid segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342 , SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, SEQ ID NO:372, SEQ ID NO:373, SEQ ID NO:374, SEQ ID NO:375, SEQ ID NO:376, SEQ ID NO:377, SEQ ID NO:378, SEQ ID NO:379, SEQ ID NO:380, SEQ ID NO:381, SEQ ID NO:382, SEQ ID NO:383, SEQ ID NO:384, SEQ ID NO:385, SEQ ID NO:386, SEQ ID NO:387, SEQ ID NO:388, SEQ ID NO:389, SEQ ID NO:390, SEQ ID NO:391, SEQ ID NO:392, SEQ ID NO:393, SEQ ID NO:394, SEQ ID NO:395, SEQ ID NO:396, SEQ ID NO:397, SEQ ID NO:398, SEQ ID NO:399, SEQ ID NO:400, SEQ ID NO:401, SEQ ID NO:402, SEQ ID NO:403, SEQ ID NO:404, SEQ ID NO:405, SEQ ID NO:406, SEQ ID NO:407, SEQ ID NO:4083, SEQ ID NO:409, SEQ ID NO:410, SEQ ID NO:411, SEQ ID NO:412, SEQ ID NO:413, SEQ ID NO:414, SEQ ID NO:415, SEQ ID NO:416, SEQ ID NO:417, SEQ ID NO:418, SEQ ID NO:419, SEQ ID NO:420, SEQ ID NO:421, SEQ ID NO:422, SEQ ID NO:423, SEQ ID NO:424, SEQ ID NO:425, SEQ ID NO:426, SEQ ID NO:427, SEQ ID NO:428, SEQ ID NO:429, SEQ ID NO:430, SEQ ID NO:431, SEQ ID NO:432, SEQ ID NO:433, SEQ ID NO:434, SEQ ID NO:435, and SEQ ID NO:436.

49. The isolated polynucleotide of claim 46, wherein said at least a first nucleic acid segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:437, SEQ ID NO:438, SEQ ID NO:439, SEQ ID NO:440, SEQ ID NO:441, SEQ ID NO:442, SEQ ID NO:443, SEQ ID NO:444, SEQ ID NO:445, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID

NO:[illegible], SEQ ID NO:[illegible], SEQ ID NO:[illegible], SEQ ID NO:[illegible], SEQ ID NO:[illegible], SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, SEQ ID NO:484, SEQ ID NO:485, SEQ ID NO:486, SEQ ID NO:487, SEQ ID NO:488, SEQ ID NO:489, SEQ ID NO:490, SEQ ID NO:491, SEQ ID NO:492, SEQ ID NO:493, SEQ ID NO:494, SEQ ID NO:495, SEQ ID NO:496, SEQ ID NO:497, SEQ ID NO:498, SEQ ID NO:499, SEQ ID NO:500, SEQ ID NO:501, SEQ ID NO:502, SEQ ID NO:503, SEQ ID NO:504, SEQ ID NO:505, SEQ ID NO:506, SEQ ID NO:507, SEQ ID NO:508, SEQ ID NO:509, SEQ ID NO:510, SEQ ID NO:511, SEQ ID NO:512, SEQ ID NO:513, SEQ ID NO:514, SEQ ID NO:515, SEQ ID NO:516, SEQ ID NO:517, SEQ ID NO:518, SEQ ID NO:519, SEQ ID NO:520, SEQ ID NO:521, SEQ ID NO:522, SEQ ID NO:523, SEQ ID NO:524, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, and SEQ ID NO:528.

50. The isolated polynucleotide of claim 46, wherein said at least a first nucleic acid segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, and SEQ ID NO:610.

51. The isolated polynucleotide of claim 46, wherein said at least a first nucleic acid segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625, SEQ ID NO:626, SEQ ID NO:627, SEQ ID NO:628, SEQ ID NO:629, SEQ ID NO:630, SEQ ID NO:631, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:634, SEQ ID NO:635, SEQ ID NO:636, SEQ ID NO:637, SEQ ID NO:638, SEQ ID NO:639, SEQ ID NO:640, SEQ ID NO:641, SEQ ID NO:642, SEQ ID NO:643, SEQ ID NO:644, SEQ ID NO:645, SEQ ID NO:646, SEQ ID NO:647, SEQ ID NO:648, SEQ ID NO:649, SEQ ID NO:650, SEQ ID NO:651, SEQ ID NO:652, SEQ ID NO:653, SEQ ID NO:654, SEQ ID NO:655, SEQ ID NO:656, SEQ ID NO:657, SEQ ID NO:658, SEQ ID NO:659, SEQ ID NO:660, SEQ ID NO:661, SEQ ID NO:662, SEQ ID NO:663, and SEQ ID NO:664.

52. The isolated polynucleotide of claim 41, wherein said at least a first nucleic acid segment is operably positioned under the control of at least a first heterologous promoter.

53. The isolated polynucleotide of claim 41, further comprising at least a second nucleic acid segment that encodes at least a second isolated **peptide** or **polypeptide**.

54. The isolated polynucleotide of claim 53, wherein said polynucleotide comprises said at least a first isolated nucleic acid segment operably attached, in frame, to said at least a second isolated nucleic acid segment, said polynucleotide encoding a fusion protein in which said first isolated **peptide** or **polypeptide** is linked to said second isolated **peptide** or **polypeptide**.

55. The isolated polynucleotide of claim 54, wherein said at least a second isolated nucleic acid segment encodes: (a) an adjuvant **peptide** or **polypeptide**, (b) an immunostimulant **peptide** or **polypeptide**, or (c) at least a second distinct **peptide** or **polypeptide** that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

56. The isolated polynucleotide of claim 41, wherein said at least a first nucleic acid segment is comprised within a vector.

57. The isolated polynucleotide of claim 41, wherein said polynucleotide is comprised within a host cell.

58. A vector comprising the isolated polynucleotide of claim 41.

59. The vector of claim 58, wherein said vector is a plasmid or viral vector.

60. An isolated host cell comprising the isolated polynucleotide of claim 41, or the vector of claim 58.

61. The isolated host cell of claim 60, wherein said host cell is an isolated human blood or bone marrow cell.

62. The isolated host cell of claim 61, wherein said human blood or bone marrow cell is isolated from a patient having, suspected of having, or at risk for developing a hematological malignancy selected from the group consisting of Hodgkin's lymphoma, follicular lymphoma, B cell-type non-Hodgkin's lymphoma, T cell-type non-Hodgkin's lymphoma, lymphoma, and chronic lymphocytic leukemia.

63. An isolated antigen-presenting cell that expresses the **peptide** or **polypeptide** of claim 1, wherein said cell is obtained from a patient having, suspected of having, or at risk for developing a hematological malignancy selected from the group consisting of leukemia and lymphoma.

64. A plurality of isolated T cells that specifically react with the **peptide** or **polypeptide** of claim 1, wherein said cells are obtained from a patient having, suspected of having, or at risk for developing a hematological malignancy selected from the group consisting of leukemia and lymphoma.

65. The plurality of isolated T cells of claim 64, wherein said cells are stimulated or expanded by contacting said cells with the **peptide** or **polypeptide** of claim 1.

66. The plurality of isolated T cells of claim 65, wherein said cells are cloned prior to expansion.

67. The plurality of isolated T cells of claim 64, wherein said cells are obtained from bone marrow, a bone marrow fraction, peripheral blood, or a peripheral blood fraction of a patient having, suspected of having, or at risk for developing a hematological malignancy selected from the group consisting of leukemia and lymphoma.

68. A composition comprising the isolated polynucleotide of claim 41, the vector of claim 58, the isolated host cell of claim 60, the isolated antigen-presenting cell of claim 63, or the plurality of isolated T cells of claim 64.

69. The composition of claim 68, further comprising a pharmaceutically-acceptable diluent.

70. The composition of claim 69, wherein said composition is formulated for parenteral, intravenous, intraarterial, intraosseus, intrathecal,

intraperitoneal, subcutaneous, intramuscular, transdermal, sublingual, or oral administration.

71. The composition of claim 71, further comprising at least a first immunostimulant or at least a first adjuvant.

72. The composition of claim 71, further comprising at least a first immunostimulant or at least a first adjuvant selected from the group consisting of Montanide ISA50, Seppic Montanide ISA720, a cytokine, a microsphere, a dimethyl dioctadecyl ammonium bromide adjuvant, AS-1, AS-2, Ribi Adjuvant, QS21, saponin, microfluidized Syntex adjuvant, MV, ddMV, an immune stimulating complex and an inactivated toxin.

73. The composition of claim 68, further comprising at least a first detection reagent.

74. The composition of claim 68, further comprising at least a first therapeutic agent.

75. The composition of claim 68, further comprising at least a first anti-cancer agent used in the treatment of Hodgkin's lymphoma, follicular lymphoma, B cell-type non-Hodgkin's lymphoma, T cell-type non-Hodgkin's lymphoma, lymphoma, or chronic lymphocytic leukemia.

76. A composition comprising: (a) at least a first isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532; and (b) at least a second distinct isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

77. The composition of claim 76, further comprising at least a third distinct isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

78. A composition comprising: (a) at least a first isolated polynucleotide that encodes a first isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532; and (b) at least a second distinct isolated polynucleotide that encodes a second distinct isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

79. The composition of claim 78, further comprising at least a third distinct isolated polynucleotide that encodes a third distinct isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

80. A composition comprising: (a) at least a first isolated polynucleotide that encodes a first isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532; and (b) at least a second distinct isolated **peptide** or **polypeptide** comprising at least a first coding region that comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

81. A hybridoma cell line that produces a monoclonal antibody having immunospecificity for the **peptide** or **polypeptide** of claim 1.

82. An isolated antibody, or an antigen-binding fragment thereof, that has immunospecificity for a **peptide** or **polypeptide** consisting essentially of the sequence of any one of SEQ ID NO:669 to SEQ ID NO:2532.

83. The antibody of claim 82, wherein said antigen-binding fragment comprises a light chain variable region, a heavy-chain variable region, a Fab fragment, a $F(ab)_2$ fragment, an Fv fragment, an scFv fragment, or an antigen-binding fragment of said antibody.

84. A kit comprising: (a) the **peptide** or **polypeptide** of claim 1, the polynucleotide of claim 41, the vector of claim 58, the host cell of claim 60, the antigen presenting cell of claim 63, the plurality of T cells of claim 64, the composition of claim 76, the composition of claim 78, the composition of claim 80, the hybridoma cell line of claim 81, or the antibody or antigen binding fragment of claim 82; and (b) instructions for using said kit in the diagnosis, detection, or treatment of at least a first hematological malignancy selected from the group consisting of Hodgkin's lymphoma, follicular lymphoma, B cell-type non-Hodgkin's lymphoma, T cell-type non-Hodgkin's lymphoma, lymphoma, and chronic lymphocytic leukemia.

85. The kit of claim 84, wherein said kit further comprises a therapeutically effective amount of at least a second anti-cancer agent.

86. A method of generating an immune response in an animal, comprising providing to said animal an effective amount of the **peptide** or **polypeptide** of claim 1, the polynucleotide of claim 41, the vector of claim 58, the host cell of claim 60, the antigen presenting cell of claim 63, or the plurality of T cells of claim 64.

87. A method of generating a T-cell response in an animal, comprising providing to said animal an effective amount of the **peptide** or **polypeptide** of claim 1, the polynucleotide of claim 41, the vector of claim 58, the host cell of claim 60, or the antigen presenting cell of claim 63.

88. The method of claim 86 or 87, wherein said animal is a human having, suspected of having, or at risk for developing a hematological malignancy selected from the group consisting of Hodgkin's lymphoma, follicular lymphoma, B cell-type non-Hodgkin's lymphoma, T cell-type non-Hodgkin's lymphoma, lymphoma, and chronic lymphocytic leukemia.

89. A method of assessing the risk of a human patient in developing a hematological malignancy selected from the group consisting of Hodgkin's lymphoma, follicular lymphoma, B cell-type non-Hodgkin's lymphoma, T cell-type non-Hodgkin's lymphoma, and lymphoma; said method comprising detecting the presence of the **peptide** or **polypeptide** of claim 1, the polynucleotide of claim 41, or the antibody of claim 82, in a clinical sample obtained from said patient, wherein an increased level of said **peptide**, **polypeptide**, polynucleotide, or antibody relative to an unaffected human is indicative of an increased risk for developing said hematological malignancy.

90. A method of detecting a Hodgkin's lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or an antigen binding fragment thereof, or in a biological sample or an animal cell said method comprising, contacting a sample or a cell suspected of containing a Hodgkin's lymphoma hematological malignancy with: (a) a labeled **peptide** or **polypeptide** according to claim 12 or 27, (b) a labeled antibody, or a labeled antigen binding fragment thereof, that is immunospecific for the **peptide** or **polypeptide** of claim 12 or 27, (c)

a labeled polynucleotide according to claim 47, or (d) a labeled polynucleotide that comprises the sequence of any of one SEQ ID NO:665 to SEQ ID NO:668, or SEQ ID NO:2533 through SEQ ID NO:9597, under conditions effective and for a time sufficient to allow immunocomplexes or specific hybridization complexes to form, wherein the presence of labeled immunocomplexes or labeled hybridization complexes is indicative of the presence of said Hodgkin's lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or antigen binding fragment in said sample or said cell.

91. A method of detecting a follicular lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or an antigen binding fragment thereof, or in a biological sample or an animal cell said method comprising, contacting a sample or a cell suspected of containing a follicular lymphoma hematological malignancy with: (a) a labeled **peptide** or **polypeptide** according to claim 15 or 28, (b) a labeled antibody, or a labeled antigen binding fragment thereof, that is immunospecific for the **peptide** or **polypeptide** of claim 15 or 28, (c) a labeled polynucleotide according to claim 48, or (d) a labeled polynucleotide that comprises the sequence of any of one SEQ ID NO:665 to SEQ ID NO:668, or SEQ ID NO:2533 through SEQ ID NO:9597, under conditions effective and for a time sufficient to allow immunocomplexes or specific hybridization complexes to form, wherein the presence of labeled immunocomplexes or labeled hybridization complexes is indicative of the presence of said follicular lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or antigen binding fragment in said sample or said cell.

92. A method of detecting a B cell non-Hodgkin's lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or an antigen binding fragment thereof, or in a biological sample or an animal cell said method comprising, contacting a sample or a cell suspected of containing a B cell non-Hodgkin's lymphoma hematological malignancy with: (a) a labeled **peptide** or **polypeptide** according to claim 18 or 29, (b) a labeled antibody, or a labeled antigen binding fragment thereof, that is immunospecific for the **peptide** or **polypeptide** of claim 18 or 29, (c) a labeled polynucleotide according to claim 49, or (d) a labeled polynucleotide that comprises the sequence of any of one SEQ ID NO:665 to SEQ ID NO:668, or SEQ ID NO:2533 through SEQ ID NO:9597, under conditions effective and for a time sufficient to allow immunocomplexes or specific hybridization complexes to form, wherein the presence of labeled immunocomplexes or labeled hybridization complexes is indicative of the presence of said B cell non-Hodgkin's lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or antigen binding fragment in said sample or said cell.

93. A method of detecting a T cell non-Hodgkin's lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or an antigen binding fragment thereof, or in a biological sample or an animal cell said method comprising, contacting a sample or a cell suspected of containing a T cell non-Hodgkin's lymphoma hematological malignancy with: (a) a labeled **peptide** or **polypeptide** according to claim 21 or 30, (b) a labeled antibody, or a labeled antigen binding fragment thereof, that is immunospecific for the **peptide** or **polypeptide** of claim 21 or 30, (c) a labeled polynucleotide according to claim 50, or (d) a labeled polynucleotide that comprises the sequence of any of one SEQ ID NO:665 to SEQ ID NO:668, or SEQ ID NO:2533 through SEQ ID NO:9597, under conditions effective and for a time sufficient to allow immunocomplexes or specific hybridization complexes to form, wherein the presence of labeled immunocomplexes or labeled hybridization complexes is indicative of the presence of said T cell non-Hodgkin's lymphoma hematological malignancy-related **polypeptide**, polynucleotide, antibody, or antigen binding fragment in said sample or said cell.

94. A method of detecting a lymphoma-related malignancy **polypeptide**, polynucleotide, antibody, or an antigen binding fragment thereof, or in

a biological sample of an animal cell said method comprising, contacting a sample or a cell suspected of containing a lymphoma-related malignancy with: (a) a labeled **peptide** or **polypeptide** according to claim 24 or 31, (b) a labeled antibody, or a labeled antigen binding fragment thereof, that is immunospecific for the **peptide** or **polypeptide** of claim 24 or 31, (c) a labeled polynucleotide according to claim 51, or (d) a labeled polynucleotide that comprises the sequence of any of one SEQ ID NO:665 to SEQ ID NO:668, or SEQ ID NO:2533 through SEQ ID NO:9597, under conditions effective and for a time sufficient to allow immunocomplexes or specific hybridization complexes to form, wherein the presence of labeled immunocomplexes or labeled hybridization complexes is indicative of the presence of said lymphoma-related malignancy-related **polypeptide**, polynucleotide, antibody, or antigen binding fragment in said sample or said cell.

95. A method for detecting antibodies specific for a hematological malignancy-related **peptide** or **polypeptide** in a biological sample, said method comprising the steps of: (a) contacting a first biological sample suspected of containing said antibodies with the **peptide** or **polypeptide** of claim 1; (b) incubating said sample under conditions effective and for a time sufficient to allow immunocomplexes to form; and (c) detecting immunocomplexes formed between said **peptide** or **polypeptide** and antibodies in said sample that are specific for said **peptide** or **polypeptide**, wherein the presence of said immunocomplexes is indicative of the presence of said antibodies in said sample.

96. A method for detecting antibodies specific for a Hodgkin's lymphoma-specific hematological malignancy-related **peptide** or **polypeptide** in a biological sample, said method comprising the steps of: (a) contacting a first biological sample suspected of containing said antibodies with the **peptide** or **polypeptide** of claim 12 or 27; (b) incubating said sample under conditions effective and for a time sufficient to allow immunocomplexes to form; and (c) detecting immunocomplexes formed between said **peptide** or **polypeptide** and antibodies in said sample that are specific for said **peptide** or **polypeptide**, wherein the presence of said immunocomplexes is indicative of the presence of said antibodies in said sample.

97. A method for detecting antibodies specific for a follicular lymphoma-specific hematological malignancy-related **peptide** or **polypeptide** in a biological sample, said method comprising the steps of: (a) contacting a first biological sample suspected of containing said antibodies with the **peptide** or **polypeptide** of claim 15 or 28; (b) incubating said sample under conditions effective and for a time sufficient to allow immunocomplexes to form; and (c) detecting immunocomplexes formed between said **peptide** or **polypeptide** and antibodies in said sample that are specific for said **peptide** or **polypeptide**, wherein the presence of said immunocomplexes is indicative of the presence of said antibodies in said sample.

98. A method for detecting antibodies specific for a B cell non-Hodgkin's lymphoma-specific hematological malignancy-related **peptide** or **polypeptide** in a biological sample, said method comprising the steps of: (a) contacting a first biological sample suspected of containing said antibodies with the **peptide** or **polypeptide** of claim 18 or 29; (b) incubating said sample under conditions effective and for a time sufficient to allow immunocomplexes to form; and (c) detecting immunocomplexes formed between said **peptide** or **polypeptide** and antibodies in said sample that are specific for said **peptide** or **polypeptide**, wherein the presence of said immunocomplexes is indicative of the presence of said antibodies in said sample.

99. A method for detecting antibodies specific for a T cell non-Hodgkin's lymphoma-specific hematological malignancy-related **peptide** or **polypeptide** in a biological sample, said method

comprising the steps of: (a) contacting a test biological sample suspected of containing said antibodies with the **peptide** or **polypeptide** of claim 21 or 30; (b) incubating said sample under conditions effective and for a time sufficient to allow immunocomplexes to form; and (c) detecting immunocomplexes formed between said **peptide** or **polypeptide** and antibodies in said sample that are specific for said **peptide** or **polypeptide**, wherein the presence of said immunocomplexes is indicative of the presence of said antibodies in said sample.

100. A method for detecting antibodies specific for a lymphoma-specific hematological malignancy-related **peptide** or **polypeptide** in a biological sample, said method comprising the steps of: (a) contacting a first biological sample suspected of containing said antibodies with the **peptide** or **polypeptide** of claim 24 or 31; (b) incubating said sample under conditions effective and for a time sufficient to allow immunocomplexes to form; and (c) detecting immunocomplexes formed between said **peptide** or **polypeptide** and antibodies in said sample that are specific for said **peptide** or **polypeptide**, wherein the presence of said immunocomplexes is indicative of the presence of said antibodies in said sample.

L12 ANSWER 25 OF 38 USPATFULL on STN
2002:337964 Compositions and methods for the therapy and diagnosis of Her-2/neu-associated malignancies.
Hand-Zimmermann, Susan, Redmond, WA, UNITED STATES
Cheever, Martin A., Mercer Island, WA, UNITED STATES
Foy, Teresa M., Federal Way, WA, UNITED STATES
Lodes, Michael J., Seattle, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Corixa Corporation, Seattle, WA, UNITED STATES, 98104 (U.S. corporation)
US 2002193329 A1 20021219
APPLICATION: US 2001-930125 A1 20010814 (9)
PRIORITY: US 2001-270520P 20010221 (60)
US 2000-236428P 20000928 (60)
US 2000-225152P 20000814 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the therapy and diagnosis of cancer, particularly Her-2/neu-associated cancers, are disclosed. Illustrative compositions comprise one or more Her-2/neu **polypeptides**, immunogenic portions thereof, polynucleotides that encode such **polypeptides**, antigen presenting cell that expresses such **polypeptides**, and T cells that are specific for cells expressing such **polypeptides**. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of Her-2/neu-associated malignancies.
CLM What is claimed is:
1. An isolated polynucleotide composition effective for eliciting an immune response in a patient, said polynucleotide encoding a **polypeptide** comprising an amino acid sequence consisting essentially of SEQ ID NO: 3.

2. An isolated **polypeptide** composition effective for eliciting an immune response, said **polypeptide** comprising an amino acid sequence consisting essentially of SEQ ID NO: 3.

3. A pharmaceutical composition comprising a polynucleotide according to claim 1 or a **polypeptide** according to claim 2, in combination with a pharmaceutically acceptable carrier.

4. The pharmaceutical composition of claim 3, further comprising an immunostimulant.

5. The pharmaceutical composition of claim 4, wherein the immunostimulant comprises an adjuvant.

6. A method for eliciting an immune response in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 1.

7. The method according to claim 6, wherein the patient is HLA-B44 positive.

8. The method according to claim 6, wherein the patient is afflicted with breast cancer.

9. A method for eliciting an immune response in a patient, comprising administering to a patient an effective amount of a polynucleotide having a sequence from about nucleotides 2026-3765 of SEQ ID NO:1.

10. The method according to claim 9, wherein the patient is afflicted with breast cancer.

11. An isolated polynucleotide composition comprising the **TCR**-alpha sequence set forth in SEQ ID NO: 13.

12. An isolated polynucleotide composition comprising the **TCR**-beta sequence set forth in SEQ ID NO: 12.

L12 ANSWER 26 OF 38 USPATFULL on STN
2002:332609 Complex-forming proteins.
Jerome, Valerie, Colbe, GERMANY, FEDERAL REPUBLIC OF
Sedlacek, Hans-Harald, Marburg, GERMANY, FEDERAL REPUBLIC OF
Muller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF
Aventis Pharma Deutschland GmbH, Frankfurt, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
US 6495346 B1 20021217
APPLICATION: US 2000-481593 20000112 (9)
PRIORITY: DE 1999-19900743 19990112
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a complex of specifically complex-forming proteins which are not naturally occurring, comprising the following components: a) at least one ligand specific for a target structure, b) at least one protein comprising a mutated dimerization domain, the mutated dimerization domain having been derived by mutation of a naturally occurring dimerization domain, it being possible for this mutated dimerization domain to interact specifically with component c) and the component b) being connected covalently to the component a), c) at least one protein comprising a mutated dimerization domain, the mutated dimerization domain having been derived by mutation of a naturally occurring dimerization domain, it being possible for this mutated dimerization domain to interact specifically with component b) and the component c) is linked covalently to the component d), and d) at least one effector. In addition, the invention relates to the use and preparation of these complexes, and to nucleic acid constructs coding for the proteins mentioned and use thereof.
CLM What is claimed is:
1. A complex comprising the following components: a) at least one ligand specific for a target structure; b) at least one protein comprising a mutated dimerization domain obtained by mutation of a naturally occurring dimerization domain, wherein said mutated dimerization domain binds specifically with component c) and said component b) is covalently bonded to said component a); c) at least one protein comprising a mutated dimerization domain obtained by mutation of a naturally occurring dimerization domain, wherein said mutated dimerization domain binds specifically with said component b) and said component c) is covalently bonded to component d); and d) at least one effector; wherein

said components b) and c) are not naturally occurring proteins, and wherein said components b) and c) are mutated binding domains of c-fos and c-jun, comprising the following mutations: c-fos amino acid 167E→K 172E→K 181E→K cjun amino acid 283K→E 288K→E 302K→E.

2. The complex as claimed in claim 1, wherein said component a) is replaced by said component d).

3. The complex as claimed in claim 1, wherein said component d) is replaced by said component a).

4. The complex as claimed in claim 1, which further comprises a fusogenic **peptide** or a translocalization **peptide**.

5. The complex as claimed in claim 1, which further comprises a cleavage sequence for a protease between said components c) and d) or a) and b).

6. The complex as claimed in claim 1, wherein said component a) is selected from the group consisting of: a growth factor, a cytokine, TNF, a chemokine, a **peptide** hormone, a mediator, a steroid hormone, a vitamin, a complement factor, a clotting factor, a kinin system factor, a fibrinolysis system factor, a plasmatic enzyme, a cell enzyme, a plasmatic enzyme inhibitor, a cell enzyme inhibitor, a virus coat protein, a cell receptor for the afore-mentioned molecules, an antibody, an antibody cleavage produce, a DNA binding protein, a DNA binding domain of a transcription factor and an activation domain of a transcription factor.

7. The complex as claimed in claim 1, wherein said component d) is selected from the group consisting of: inhibitors of cell proliferation, apoptosis-inducing proteins, cytostatic proteins, cytotoxic proteins, coagulation-inducing factors, angiogenesis-inducing factors, angiogenesis-inhibiting factors, growth factors, cytokines, chemokines, interleukins, interferons, complement factors, clotting factors, fibrinolysis-inducing proteins, **peptide** hormones, mediators, bacterial proteins, receptors, viral antigens, parasitic antigens, tumor antigens, autoantigens, tissue antigens, adhesion molecules, antibodies, antibody cleavage products, enzymes for reacting with a signal-emitting component, enzymes for converting a precursor of an active substance into an active substance, fluorescent dyes, isotopes, metal-binding proteins, and a DNA-binding domain.

8. The complex as claimed in claim 6, wherein said antibody cleavage product is selected from the group consisting of: $F(ab)_2$, a single-chain Fv, a single-chain, a double antigen-binding molecule, and an Fc fragment.

9. The complex as claimed in claim 7, wherein said receptor is selected from the group consisting of receptors for: growth factors, cytokines, chemokines, interleukins, interferons, complement factors, clotting factors, fibrinolysis-inducing proteins, **peptide** hormones, steroid hormones, mediators, and virus coat proteins.

10. The complex as claimed in claim 7, wherein said antibody cleavage product is selected from the group consisting of: $F(ab)_2$, Fab, single-chain Fv, and single-chain double antigen-binding proteins.

11. The complex as claimed in claim 1, wherein at least one protein of component b) binds specifically with at least one protein of component c) with a binding constant of at least a K_M of 10^{-7} mol l^{-1}.

12. A vaccine comprising the complex as claimed in claim 1.

L12 ANSWER 27 OF 38 USPATFULL on STN
2002:315069 Compositions and methods for treatment of neoplastic disease.
Terman, David S., Pebble Beach, CA, UNITED STATES
US 2002177551 A1 20021128
APPLICATION: US 2001-870759 A1 20010530 (9)
PRIORITY: US 2000-208128P 20000531 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention comprises compositions and methods for treating a tumor or neoplastic disease in a host, The methods employ conjugates comprising superantigen **polypeptides**, nucleic acids with other structures that preferentially bind to tumor cells and are capable of inducing apoptosis. Also provided are superantigen-glycolipid conjugates and vesicles that are loaded onto antigen presenting cells to activate both T cells and NKT cells. Cell-based vaccines comprise tumor cells engineered to express a superantigen along with glycolipids products which, when expressed, render the cells capable of eliciting an effective anti-tumor immune response in a mammal into which these cells are introduced. Included among these compositions are tumor cells, hybrid cells of tumor cells and accessory cells, preferably dendritic cells. Also provided are tumoricidal T cells and NKT cells devoid of inhitory receptors or inhibitory signaling motifs which are hyperresponsive to the the above compositions and lipid-based tumor associated antigens that can be administered for adoptive immunotherapy of cancer and infectious diseases.

CLM What is claimed is:

1. A mammalian cell receptor useful in the treatment of cancer which binds tumor associated lipids wherein said binding induces anergy or apoptosis in said T cells and antigen presenting cells.

2. The tumor associated lipids of claim 1 which are selected from a group consisting of fatty acids, ceramides, glycolipids, sphingolipids, glycosphingolipids, phosphosphingolipids, gangliosides, sialylated glycans, lipopeptides and proteoglycolipids.

3. The mammalian cells of claims 1 and 2 which are selected from a group consisting of T cells, NKT cells, antigen presenting cells, dendritic cells, fibroblasts, macrophages.

4. The cells of claim 1 and 3 which have a conserved sequence tyrosine-based inhibitory motif sequence in their cytoplasmic tails

5. A mammalian cell useful in the treatment of cancer in a mammal wherein the receptor which binds tumor associated lipids and induces cellular inactivation or death is deleted or functionally deactivated.

6. The cells of claim 5 which are selected from a group consisting of T cells, NKT cells, antigen presenting cells, dendritic cells, fibroblasts, macrophages

7. A method for producing a tumoricidal immunocyte population in vivo in a mammal said method comprising allowing tumor associated lipids to contact immunocytes in which receptors for immunosuppressive fatty acids, ceramides, glycolipids, sphingolipids, glycosphingolipids, phosphosphingolipids, gangliosides, sialylated glycans, lipopeptides and proteoglycolipids. are inactivated or deleted.

8. A method for producing a tumoricical immunocyte population ex vivo in a mammal, said method comprising: a) allowing tumor associated lipids to contact immunocytes in which receptors for said lipids are inactivated or deleted to produce a tumoricidal immunocyte population. b) administering said tumoricidally activated immunocytes to the host.

9. A method for producing a tumoricical antigen presenting cell population ex vivo in a mammal, said method comprising: a) allowing a

tumor associated lipid to contact antigen presenting cells in which receptors for said tumor associated lipids are inactivated or deleted to produce a tumoricidally activated population. b) administering said antigen presenting cells to the host.

10. A method for producing a tumoricical T cell population ex vivo in a mammal, said method comprising: a) allowing a tumor associated lipids to contact T cells in which adaptor proteins which inhibit T cell activation by tumor associated antigens are deleted or functionally deactivated to produce a tumoricidal population of T cells. b) administering said tumoricidally activated T cells to the host.

11. A method of treating cancer in a mammal by administration of a lipid binding molecule which binds immunosuppressive tumor associated lipids in vivo.

12. A method of treating cancer in a mammal wherein the lipid binding molecules are administered to the host 1-4 hours before the administration of tumoricidally activated cells of claims 5 and 6.

13. The lipid binding protein of claim 11 which is selected from a group consisting of sialic acic binding lectin (Siglecs), prosaposin, saposins and glycolipid transfer protein (GLTP).

14. A construct useful in the treatment of cancer comprising a superantigen nucleotide inserted into a virus.

15. The virus claim 14 wherein said virus contains a tissue specific promoter

16. The virus of claim 15 wherein the tissue specific promoter is selected from a group consisting of prostate specific promoter, albumin specific promoter, myeloma immunogloulin specific promoter, alpha fetoprotein promoter.

17. The virus of claim 14 wherein said virus is deleted of a tumor suppressor inactivating gene.

18. The virus of claim 17 wherein said tumor specific promoter is an adenoviral mutant (dl1150) which lacks expression of the E1B-55-kDA protein.

19. The virus of claim 14 wherein the virus encodes an immunogenic cell surface protein

20. The virus of claim 19 wherein the cell surface protein is HSV-E6 or E7.

21. The virus of claim 14 wherein said virus contains a prodrug enzyme.

22. The virus of claim 21 wherein said virus contains a herpes simplex virus thymidine kinase gene

23. The virus of claim 14 wherein said virus contains a self replicating RNA sequence.

24. The virus of claim 23 wherein said virus is an Alphavirus producing tumor encoding tumor specific antigens, superantigens and lipid binding agents.

25. A mammalian T cell useful in the treatment of cancer wherein an adaptor protein which inhibits T cell activation by tumor associated antigens is deleted or functionally deactivated.

26. A method for producing a tumoricidal T cell population in vivo in a mammal said method comprising allowing a tumor associated antigen and to

activation by tumor associated antigens are deleted or functionally deactivated.

27. A composition useful in the treatment of cancer comprising a lipid raft conjugated to a superantigen.

28. The composition of claim 27 wherein said lipid raft comprises signal transduction molecules, G proteins, cell surface receptors, tumor associated antigens.

29. A method for producing a tumoricical T cell population ex vivo in a mammal, said method comprising: said method comprising allowing a superantigen-lipid raft conjugate to contact immunocytes in vivo

30. A method for producing a tumoricical T cell population ex vivo in a mammal, said method comprising: a) allowing a superantigen-lipid raft to contact T cells ex vivo b) administering said tumoricidally activated T cells to the host.

L12 ANSWER 28 OF 38 USPATFULL on STN
2002:314394 Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein.
Gaur, Amitabh, San Diego, CA, UNITED STATES
Conlon, Paul, Solana Beach, CA, UNITED STATES
Ling, Nicholas C., San Diego, CA, UNITED STATES
Staehelin, Theophil, Arelsheim, SWITZERLAND
Crowe, Paul D., Encinitas, CA, UNITED STATES
Neurocrine Biosciences, Inc., San Diego, CA, UNITED STATES, 92121-1102 (U.S. corporation)
US 2002176866 A1 20021128
APPLICATION: US 2002-104973 A1 20020320 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed toward **peptide** analogs of human myelin basic protein. The **peptide** analog is at least seven amino acids long and derived from residues 83 to 99 of human myelin basic protein. The analogs are altered from the native sequence at least at positions 91, 95, or 97. Additional alterations may be made at other positions Pharmaceutical compositions containing these **peptide** analogs are provided. The **peptide** analogs are useful for treating multiple sclerosis.
CLM What is claimed is:
1. A method for inducing a **Th2** immune response to myelin basic protein or a **peptide** analog thereof in a patient, comprising: administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a **peptide** analog selected from the group consisting of: (a) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid, and one to three L-amino acids selected from the group consisting of valine at position 86, valine at position 87, histidine at position 88, threonine at position 95, threonine at position 98 and proline at position 99 are altered to an amino acid other than the amino acid present in the native protein at that position; (b) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 97, wherein the L-arginine at position 97 is altered to another amino acid and one to three L-amino acids selected from the group consisting of valine at position 86, valine at position 87, histidine at position 88, threonine at position 95, threonine at position 98 and proline at position 99 are altered to an amino acid other than the amino acid present in the native protein at that position; (c) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 95, wherein the

L-threonine at position 95 is altered to another amino acid and one to three L-amino acids selected from the group consisting of valine at position 86, valine at position 87, histidine at position 88, threonine at position 98 and proline at position 99 are altered to an amino acid other than the amino acid present in the native protein at that position; (d) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid and the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid, such that upon administration of the **peptide** analog in vivo proteolysis is reduced; (e) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 95, wherein the L-lysine at position 91 is altered to another amino acid and the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid, such that upon administration of the **peptide** analog in vivo proteolysis is reduced; (f) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 97, wherein the L-lysine at position 91 is altered to another amino acid and the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid, such that upon administration of the **peptide** analog in vivo proteolysis is reduced; (g) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid; (h) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 95, wherein the L-threonine at position 95 is altered to another amino acid; and (i) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 97, wherein the L-arginine at position 97 is altered to another amino acid; wherein the **peptide** analog is administered in combination with a physiologically acceptable carrier/adjuvant or diluent.

2. A method according to claim 1, wherein L-lysine at position 91 is altered to a non-conservative amino acid.

3. A method according to claim 1, wherein residue 91 is altered to D-lysine.

4. A method according to claim 1, wherein residue 91 is altered to an amino acid selected from the group consisting of arginine, asparagine, histidine, leucine, serine, glycine, glutamic acid, phenylalanine, alanine and D-lysine.

5. A method according to claim 1, wherein residue 91 is altered to alanine and residue 87 is altered to D-valine.

6. A method according to claim 1, wherein residue 91 is altered to alanine and residue 88 is altered to D-histidine.

7. A method according to claim 1, wherein residue 91 is altered to alanine and residue 99 is altered to D-proline.

8. A method according to claim 1, wherein residue 91 is altered to alanine, residue 87 is altered to D-valine, and residue 99 is altered to D-proline.

9. A method according to claim 1, wherein residue 91 is altered to alanine, residue 88 is altered to D-histidine, and residue 99 is altered to D-proline.

10. A method according to claim 1, wherein the L-lysine at position 91 is altered to another amino acid, and wherein residue 88 is altered to an amino acid selected from the group consisting of serine, glutamic

acid, tyrosine, leucine, D-histidine, glutamine, phenylalanine and lysine.

11. A method according to claim 1, wherein the L-arginine at position 97 is altered to a non-conservative amino acid.

12. A method according to claim 1, wherein residue 97 is altered to D-arginine.

13. A method according to claim 1, wherein residue 97 is altered to an amino acid selected from the group of D-alanine, D-arginine, glycine, lysine, glutamine, glutamic acid, threonine, leucine, phenylalanine, histidine and alanine.

14. A method according to claim 1, wherein residue 97 is altered to alanine and residue 87 is altered to D-valine.

15. A method according to claim 1, wherein residue 97 is altered to alanine and residue 88 is altered to D-histidine.

16. A method according to claim 1, wherein residue 97 is altered to alanine and residue 99 is altered to D-proline.

17. A method according to claim 1, wherein residue 97 is altered to alanine, residue 87 is altered to D-histidine and residue 99 is altered to D-proline.

18. A method according to claim 1, wherein residue 97 is altered to alanine, residue 88 is altered to D-histidine and residue 99 is altered to D-proline.

19. A method according to claim 1, wherein the L-arginine at position 97 is altered to another amino acid, and wherein residue 88 is altered to an amino acid selected from the group consisting of serine, glutamic acid, tyrosine, leucine, D-histidine, glutamine, phenylalanine and lysine.

20. A method according to claim 1, wherein the L-threonine at position 95 is altered to a non-conservative amino.

21. A method according to claim 1, wherein residue 95 is altered to D-threonine.

22. A method according to claim 1, wherein residue 95 is altered to an amino acid selected from the group consisting of alanine, D-threonine, glycine, isoleucine, tyrosine, glutamine, serine, lysine, glutamic acid and histidine.

23. A method according to claim 1, wherein residue 95 is altered to alanine and residue 87 is altered to D-valine.

24. A method according to claim 1, wherein residue 95 is altered to alanine and residue 88 is altered to D-histidine.

25. A method according to claim 1, wherein residue 95 is altered to alanine and residue 99 is altered to D-proline.

26. A method according to claim 1, wherein residue 95 is altered to alanine, residue 87 is altered to D-valine, and residue 99 is altered to D-proline.

27. A method according to claim 1, wherein residue 95 is altered to alanine, residue 88 is altered to D-histidine, and residue 99 is altered to D-proline.

28. A method according to claim 1, wherein the N-terminal and/or

29. A method according to claim 1, wherein the **peptide** analog comprises seven to seventeen amino acids.

30. A method according to claim 29, wherein the **peptide** further comprises one to three additional altered residues selected from residues 83-90, 92-96, 98 and 99 to another amino acid.

31. A method according to claim 1, wherein residue 91 is alanine, residue 88 is D-histidine and residue 99 is D-proline.

32. A method according to claim 1, wherein residue 91 is alanine, residue 87 is D-valine and residue 99 is D-proline.

33. A method according to claim 1, wherein residue 91 is alanine and residue 88 is D-histidine.

34. A method according to claim 1, wherein residue 91 is alanine and residue 87 is D-valine.

35. A method according to claim 1, wherein residue 91 is alanine and residue 99 is D-proline.

36. A method according to claim 1, wherein residue 95 is alanine, residue 87 is D-valine, and residue 99 is D-proline.

37. A method according to claim 1, wherein residue 95 is alanine, residue 88 is D-histidine and residue 99 is D-proline.

38. A method according to claim 1, wherein residue 95 is alanine and residue 88 is D-histidine.

39. A method according to claim 1, wherein residue 95 is alanine and residue 99 is D-proline.

40. A method according to claim 1, wherein residue 95 is alanine and residue 87 is D-histidine.

41. A method according to claim 1, wherein residue 97 is alanine, residue 87 is D-valine, and residue 99 is D-proline.

42. A method according to claim 1, wherein residue 97 is alanine, residue 88 is D-histidine and residue 99 is D-proline.

43. A method according to claim 1, wherein residue 97 is alanine and residue 87 is D-valine.

44. A method according to claim 1, wherein residue 97 is alanine and residue 88 is D-histidine.

45. A method according to claim 1, wherein residue 97 is alanine and residue 99 is D-proline.

46. A method for inducing a **Th2** immune response to myelin basic protein or a **peptide** analog thereof in a patient, comprising: administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a **peptide** analog, wherein the **peptide** analog comprises at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid, and two to four additional L-amino acids selected from residues 83 to 90 and 92 to 99 are altered to an amino acid other than the amino acid present in the native protein at that position, wherein the **peptide** analog is administered in combination with a physiologically acceptable carrier or diluent.

47. A method according to claim 46, wherein L-lysine at position 91 is altered to alanine.

48. A method according to claim 46, wherein the phenylalanine at position 89 is substituted with another amino acid.

49. A method according to claim 46, wherein the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid.

50. A method according to claim 46, wherein the N-terminal and/or C-terminal amino acids are altered to a D-amino acid.

51. A method according to claim 50, wherein the N-terminal amino acid is residue 83 of human myelin basic protein.

52. A method according to claim 46, wherein at least one of the additional L-amino acids selected from residues 83 to 90 and 92 to 99 is substituted with a charged amino acid.

53. A method according to claim 46, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-leucine, and L-lysine at position 91 is altered to L-alanine.

54. A method according to claim 46, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein L-glutamic acid at position 83 is altered to D-alanine, L-phenylalanine at position 89 is altered to L-alanine and L-lysine at position 91 is altered to L-alanine.

55. A method according to claim 46, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-alanine, and L-lysine at position 91 is altered to L-alanine.

56. A method according to claim 46, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-alanine, L-lysine at position 91 is altered to L-alanine, and L-threonine and position 98 is altered to D-alanine.

57. A method according to claim 46, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-leucine, L-lysine at position 91 is altered to L-alanine, and L-threonine at position 98 is altered to D-alanine.

58. A method according to claim 46, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-lysine at position 91 and the L-phenylalanine at position 89 are altered to other amino acids.

59. A method according to claim 1 or claim 47, wherein the pharmaceutical composition further comprises an adjuvant.

60. A method according to claim 59, wherein the adjuvant is alum.

61. A method for inducing a **Th2** immune response to myelin basic protein or a **peptide** analog thereof in a patient, comprising:

administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a **peptide** analog comprising the sequence D-Ala-Lys-Pro-Val-Val-His-Leu-Phe-Ala-Asn-Ile-Val-Thr-Pro-Arg-Thr-Pro (SEQ ID NO: 7).

62. A method for inducing a persistent systemic immune response to myelin basic protein or a **peptide** analog thereof in a patient, comprising: administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a **peptide** analog selected from the group consisting of (a) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid, and one to three L-amino acids selected from the group consisting of valine at position 86, valine at position 87, histidine at position 88, threonine at position 95, threonine at position 98 and proline at position 99 are altered to an amino acid other than the amino acid present in the native protein at that position; (b) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 97, wherein the L-arginine at position 97 is altered to another amino acid and one to three L-amino acids selected from the group consisting of valine at position 86, valine at position 87, histidine at position 88, threonine at position 95, threonine at position 98 and proline at position 99 are altered to an amino acid other than the amino acid present in the native protein at that position; (c) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 95, wherein the L-threonine at position 95 is altered to another amino acid and one to three L-amino acids selected from the group consisting of valine at position 86, valine at position 87, histidine at position 88, threonine at position 98 and proline at position 99 are altered to an amino acid other than the amino acid present in the native protein at that position; (d) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid and the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid, such that upon administration of the **peptide** analog in vivo proteolysis is reduced; (e) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 95, wherein the L-lysine at position 91 is altered to another amino acid and the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid, such that upon administration of the **peptide** analog in vivo proteolysis is reduced; (f) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 97, wherein the L-lysine at position 91 is altered to another amino acid and the N-terminal amino acid and/or the C-terminal amino acid are altered to another amino acid, such that upon administration of the **peptide** analog in vivo proteolysis is reduced; (g) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 91, wherein the L-lysine at position 91 is altered to another amino acid; (h) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 95, wherein the L-threonine at position 95 is altered to another amino acid; and (i) **peptide** analogs comprising at least seven amino acids selected from residues 83 to 99 of human myelin basic protein, including residue 97, wherein the L-arginine at position 97 is altered to another amino acid; wherein the **peptide** analog is administered in combination with a physiologically acceptable carrier or diluent.

63. A method according to claim 62, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is

altered to L-leucine, and L-lysine at position 91 is altered to L-alanine.

64. A method according to claim 62, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein L-glutamic acid at position 83 is altered to D-alanine, L-phenylalanine at position 89 is altered to L-alanine and L-lysine at position 91 is altered to L-alanine.

65. A method according to claim 62, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-alanine, and L-lysine at position 91 is altered to L-alanine.

66. A method according to claim 62, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-alanine, L-lysine at position 91 is altered to L-alanine, and L-threonine and position 98 is altered to D-alanine.

67. A method according to claim 62, wherein the **peptide** analog comprises residues 83 to 99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-leucine, L-lysine at position 91 is altered to L-alanine, and L-threonine at position 98 is altered to D-alanine.

L12 ANSWER 29 OF 38 USPATFULL on STN
2002:314392 Recombinant MHC molecules useful for manipulation of antigen-specific T-cells.
Burrows, Gregory G., Portland, OR, UNITED STATES
Vandenbark, Arthur A., Portland, OR, UNITED STATES
Oregon Health & Science University (U.S. corporation)
US 2002176864 A1 20021128
APPLICATION: US 2001-858580 A1 20010515 (9)
PRIORITY: US 1997-64552P 19970916 (60)
US 1997-64555P 19971010 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Two-domain MHC **polypeptides** useful for manipulation of antigen-specific T-cells are disclosed. These **polypeptides** include MHC class II-based molecules that comprise covalently linked β1 and α1 domains, and MHC class I-based molecules that comprise covalently linked α1 and α2 domains. These **polypeptides** may also include covalently linked antigenic determinants, toxic moieties, and/or detectable labels. The disclosed **polypeptides** can be used to target antigen-specific T-cells, and are useful, among other things, to detect and purify antigen-specific T-cells, to induce or activate T-cells, and to treat conditions mediated by antigen-specific T-cells.

CLM What is claimed is:

1. A purified **polypeptide** comprising, covalently linked first and second domains, wherein: (a) the first domain is a mammalian MHC class II β1 domain and the second domain is a mammalian MHC class II α1 domain; or (b) the first domain is a mammalian MHC class I α1 domain and the second domain is a mammalian MHC class I α2 domain, and wherein the **polypeptide** is not a whole MHC class I α chain; and wherein the amino terminus of the second domain is covalently linked to the carboxy terminus of the first domain.

2. The **polypeptide** of claim 1 wherein the covalent linkage between the

first and second domains is provided by a **peptide** linker sequence.

3. The **polypeptide** of claim 1 wherein the **polypeptide** further comprises, covalently linked to the amino terminus of the first domain, a third domain comprising an antigenic determinant.

4. The **polypeptide** of claim 3 wherein the antigenic determinant is a **peptide** antigen.

5. The **polypeptide** of claim 4 wherein the covalent linkage between the first and third domains is provided by a **peptide** linker sequence.

6. The **polypeptide** of claim 1 further comprising an antigenic determinant associated with the **polypeptide** by non-covalent interaction.

7. The **polypeptide** of claim 6 wherein the antigenic determinant is a **peptide** antigen.

8. The **polypeptide** of claim 1 wherein the **polypeptide** further comprises a covalently linked detectable marker or toxic moiety.

9. The **polypeptide** of claim 1 wherein the first domain is a mammalian MHC class II β1 domain and the second domain is a mammalian MHC class II α1 domain.

10. A recombinant **polypeptide** comprising α1 and β1 domains of a mammalian molecule wherein the amino terminus of the α1 domain is covalently linked to the carboxy terminus of the β1 domain.

11. The recombinant **polypeptide** according to claim 10, wherein the **polypeptide** further comprises an antigenic determinant associated with the **polypeptide** by covalent or non-covalent interaction.

12. The recombinant **polypeptide** according to claim 11 wherein the antigenic determinant is covalently linked to the amino terminus of the β1 domain.

13. The recombinant **polypeptide** according to claim 10 wherein the **polypeptide** further comprises a detectable marker or toxic moiety.

14. A recombinant **polypeptide** according to claim 1 wherein the first domain is a mammalian MHC class I α1 domain and the second domain is a mammalian MHC class I α2 domain.

15. A **polypeptide** comprising covalently joined α1 and α2 domains of a mammalian MHC class I molecule wherein the amino terminus of the α2 domain is covalently linked to the carboxy terminus of the α1 domain, and wherein the **polypeptide** does not include an MHC class I α3 domain.

16. The **polypeptide** according to claim 15, wherein the **polypeptide** further comprises an antigenic determinant associated with the **polypeptide** by covalent or non-covalent interaction.

17. The **polypeptide** according to claim 16 wherein the antigenic determinant is covalently linked to the amino terminus of the α1 domain.

18. The recombinant **polypeptide** according to claim 15 wherein the **polypeptide** further comprises a detectable marker or toxic moiety.

19. A nucleic acid molecule encoding a **polypeptide** according to claim 1.

20. A transgenic cell including a nucleic acid molecule according to claim 19.

21. A nucleic acid expression vector comprising a nucleic acid molecule according to claim 19.

22. A recombinant nucleic acid molecule, comprising first, second and third regions represented by the formula Pr-B-A, wherein: Pr is a promoter sequence; B is a coding sequence that encodes a β1 domain of a mammalian MHC class II molecule; and A is a coding sequence that encodes an a 1 domain of a mammalian MHC class II molecule; wherein Pr is operably linked to B, and B and A comprise a single open reading frame.

23. A recombinant nucleic acid molecule, comprising first, second, third and fourth regions represented by the formula Pr-P-B-A, wherein: Pr is a promoter sequence; P is a coding sequence that encodes a **peptide** antigen; B is a coding sequence that encodes a β1 domain of a mammalian MHC class II molecule; and A is a coding sequence that encodes an α1 domain of a mammalian MHC class II molecule; wherein Pr is operably linked to P, and P, B and A comprise a single open reading frame.

24. A recombinant nucleic acid molecule, comprising first, second and third regions represented by the formula Pr-B-A, wherein: Pr is a promoter sequence; B is a coding sequence that encodes an α1 domain of a mammalian MHC class I molecule; and A is a coding sequence that encodes an α2 domain of a mammalian MHC class I molecule; wherein Pr is operably linked to B, and B and A comprise a single open reading frame, and wherein the open reading frame does not encode an α3 domain of a mammalian MHC class I molecule.

25. A recombinant nucleic acid molecule, comprising first, second, third and fourth regions represented by the formula Pr-P-B-A, wherein: Pr is a promoter sequence; P is a coding sequence that encodes a **peptide** antigen; B is a coding sequence that encodes an α1 domain of a mammalian MHC class I molecule; and A is a coding sequence that encodes an α2 domain of a mammalian MHC class I molecule; wherein Pr is operably linked to P, and P, B and A comprise a single open reading frame, and wherein the open reading frame does not encode an α3 domain of a mammalian MHC class I molecule.

26. A method for detecting or quantifying in a biological sample the presence of T-cells having a receptor specific for a specified antigen, comprising: combining the biological sample with a recombinant **polypeptide** comprising covalently linked α1 and β1 domains of a mammalian MHC, class II molecule wherein the carboxy terminus of the β1 domain is covalently linked to the amino terminus of the α1 domain, and further comprising the specified antigen bound in a **peptide** binding groove formed by said α1 and β1 domains; and detecting or quantifying the presence of specific binding of the recombinant **polypeptide** with said T-cells.

27. A method for separating T-cells having a receptor specific for a specified antigen from a mixture of cells, comprising: combining the cell mixture with a recombinant **polypeptide** comprising covalently linked α1 and β1I domains of a mammalian MHC class II molecule wherein the carboxy terminus of the β1 domain is covalently linked to the amino terminus of the α1 domain, and further comprising the specified antigen bound in a **peptide** binding groove formed by said α1 and β1 domains; and separating those cells bound to the recombinant **polypeptide** from unbound cells.

28. A method for detecting or quantifying in a biological sample the

presence of T-cells having a receptor specific for a specified antigen, comprising: combining the biological sample with a **polypeptide** comprising covalently linked α1 and α2 domains of a mammalian MHC class I molecule wherein the carboxy terminus of the α1 domain is covalently linked to the amino terminus of the α2 domain, wherein the **polypeptide** does not include an α3 domain of a mammalian MHC class I molecule and wherein the **polypeptide** further comprises the specified antigen bound in a **peptide** binding groove formed by said α1 and α2 domains; and detecting or quantifying the presence of specific binding of the recombinant **polypeptide** with said T-cells.

29. A method for separating T-cells having a receptor specific for a specified antigen from a mixture of cells, comprising: combining the cell mixture with a **polypeptide** comprising covalently linked α1 and α2 domains of a mammalian MHC class I molecule wherein the carboxy terminus of the α1 domain is covalently linked to the amino terminus of the α2 domain, wherein the **polypeptide** does not include an α3 domain of a mammalian MHC class I molecule and wherein the **polypeptide** further comprises the specified antigen bound in a **peptide** binding groove formed by said α1 and α2 domains; and separating those cells bound to the recombinant **polypeptide** from unbound cells.

30. A pharmaceutical composition comprising a **polypeptide** according to claim 1 and a pharmaceutically acceptable carrier.

31. A method of inhibiting T-cell activity, comprising contacting T-cells with a **polypeptide** according to claim 3.

32. A method of treating a disease caused by antigen-specific T-cells, comprising administering to a patient a composition comprising a **polypeptide** according to claim 3.

33. A method of activating T-cells, comprising contacting T-cells with a **polypeptide** according to claim 3.

L12 ANSWER 30 OF 38 USPATFULL on STN
2002:300817 Methods of preventing or treating inflammatory or autoimmune disorders by administering integrin alphanubeta3 antagonists in combination with other prophylactic or therapeutic agents.
Dingivan, Christine, Germantown, MD, UNITED STATES
Wilder, Ronald, Rockville, MD, UNITED STATES
US 2002168360 A1 20021114
APPLICATION: US 2002-91236 A1 20020304 (10)
PRIORITY: US 2001-273098P 20010302 (60)
US 2001-316321P 20010831 (60)
US 2001-346918P 20011019 (60)
US 2002-358424P 20020219 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides to methods of preventing, treating or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder utilizing combinatorial therapy. In particular, the present invention provides methods of preventing, treating, or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder comprising administering to a subject in need thereof one or more integrin $\alpha_v\beta_3$ antagonists and at least one other prophylactic or therapeutic agent. The present invention also provides compositions and articles of manufacture for use in preventing, treating or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder.
CLM What is claimed is:

1. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of one or more integrin $\alpha_v\beta_3$ antagonists and a prophylactically or therapeutically effective amount of one or more immunomodulatory agents.

2. The method of claim 1 wherein said $\alpha_v\beta_3$ antagonist is VITAXIN.TM. or an antigen-binding fragment thereof.

3. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of one or more integrin $\alpha_v\beta_3$ antagonists and a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents.

4. The method of claim 3 wherein said $\alpha_v\beta_3$ antagonist is VITAXIN.TM. or an antigen-binding fragment thereof.

5. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of one or more integrin $\alpha_v\beta_3$ antagonists and a prophylactically or therapeutically effective amount of one or more TNF-α antagonists.

6. The method of claim 5 wherein said $\alpha_v\beta_3$ antagonist is VITAXIN.TM. or an antigen-binding fragment thereof.

7. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of one or more integrin $\alpha_v\beta_3$ antagonists and a prophylactically or therapeutically effective amount of one or more CD2 binding molecules.

8. The method of claim 7 wherein said $\alpha_v\beta_3$ antagonist is VITAXIN.TM. or an antigen-binding fragment thereof.

9. The method of claim 1 or 2, wherein at least one immunomodulatory agent is a small organic molecule.

10. The method of claim 1 or 2, wherein at least one immunomodulatory agent is a **T cell receptor** modulator or a cytokine receptor modulator.

11. The method of claim 9, wherein the small organic molecule is methotrexate, leflunomide, cyclophosphamide, cyclosporine A, FK506, mycophenolate mofetil, rapamycin, mizoribine, deoxyspergualin, brequinar, a malononitriloamide, a steroid or a corticosteriod.

12. The method of claim 10, wherein the **T cell receptor** modulator is an antibody, **peptide** or a fusion protein which immunospecifically binds to a **T cell receptor**.

13. The method of claim 12, wherein the antibody that immunospecifically binds to a **T cell receptor** is a monoclonal antibody or an antigen-binding fragment thereof.

14. The method of claim 13, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

15. The method of claim 13, wherein the monoclonal antibody is an anti-CD2 monoclonal antibody, an anti-CD4 monoclonal antibody, an anti-CD8 monoclonal antibody or an anti-CD40 monoclonal antibody.

16. The method of claim 12, wherein the fusion protein is CTLA4-Ig.

17. The method of claim 10, wherein the cytokine receptor modulator is a cytokine, a fragment of a cytokine, a fusion protein or an antibody that immunospecifically binds to a cytokine receptor.

18. The method of claim 10, wherein the cytokine receptor modulator is a **peptide**, **polypeptide**, fusion protein or an antibody that inmmunospecifically binds to a cytokine.

19. The method of claim 17, wherein the antibody that immunospecifically binds to a cytokine receptor is a monoclonal antibody or an antigen-binding fragment thereof.

20. The method of claim 19, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

21. The method of claim 17, wherein the antibody is an anti-IL-2 receptor antibody and anti-IL-12 receptor antibodies.

22. The method of claim 18, wherein the antibody that immunospecifically binds to a cytokine is a monoclonal antibody or an antigen-binding fragment thereof.

23. The method of claim 22, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

24. The method of claim 18, wherein the antibody is anti-TNF-α antibody, an anti-IL-1β antibody, or an anti-IL-6 antibody.

25. The method of claim 17, wherein the cytokine is IL-4 or IL-10.

26. The method of claim 18, wherein the **polypeptide** is a fragment of a cytokine receptor that immunospecifically binds to a cytokine.

27. The method of claim 26, wherein the fragment is a portion of the extracellular domain of a TNF-α receptor.

28. The method of claim 3 or 4, wherein at least one anti-inflammatory agent is a non-steroidal anti-inflammatory drug.

29. The method of claim 27, wherein the non-steriodal anti-inflammatory drug is aspirin, ibuprofen, diclofenac, nabumetone, naproxen, or ketoproten.

30. The method of claim 5 or 6, wherein the TNF-α antagonist is ENBREL.TM. or REMICADE.TM..

31. The method of claim 5 or 6 further comprising administering to said subject a prophylactically or therapeutically effective amount of methotrexate.

32. The method of claim 7 or 8, wherein the CD2 binding molecule is a **peptide**, **polypeptide**, fusion protein or an antibody that immunospecifically binds to a CD2 **polypeptide**.

33. The method of claim 32, wherein the fusion protein is LFA-3TIP.

34. The method of claim 7 or 8 further comprising administering to said subject a prophylactically or therapeutically effective amount of a non-steriodal anti-inflammatory drug.

35. The method of claim 34, wherein the non-steroidal anti-inflammatory drug is aspirin, ibuprofen, diclofenac, nabumetone, naproxen, or ketoproten.

36. The method of claim 7 or 8 further comprising administering to said subject a prophylactically or therapeutically effective amount of one or more immunomodulatory agents other than a CD2 binding molecule.

37. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of one or more integrin $\alpha_v\beta_3$ antagonists and a prophylactically or therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof.

38. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of VITAXIN.TM. or an antigen-binding fragment thereof and a prophylactically or therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof.

39. The method of claim 37 or 38 further comprising administering to said subject a prophylactically or therapeutically effective amount of one or more TNF-α antagonists.

40. The method of claim 37 or 38 further comprising administering to said subject a prophylactically or therapeutically effective amount of methotrexate.

41. The method of claim 37 or 38 further comprising administering to said subject a prophylactically or therapeutically effective amount of one or more TNF-α antagonists and a prophylactically or therapeutically effective amount of methotrexate.

42. The method of claim 39, wherein at least one TNF-α antagonist is ENBREL.TM. or REMICADE.TM..

43. The method of claim 1, 3, 5, 7 or 37, wherein at least one integrin $\alpha_v\beta_3$ antagonist is an anti-integrin $\alpha_v\beta_3$ antibody.

44. The method of claim 44, wherein the anti-$\alpha_v\beta_3$ antibody is a monoclonal antibody or an antigen-binding fragment thereof.

45. The method of claim 45, wherein the monoclonal antibody is a human or humanized monoclonal antibody.

46. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 37 or 38, wherein the inflammatory disorder is asthma, encephilitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), arthritis, or an allergic disorder.

47. The method of claim 1, 2, 3, 4, 7, 8, 37 or 38, wherein the autoimmune disorder is rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's Syndrome, inflammatory bowel disease associated arthritis, an undifferentitated spondyloarthropathy, psoriasis, or an undifferentiated arthropathy.

48. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 37 or 38, wherein the subject is a human.

49. The method of claim 5, 6, 7, 8, 37 or 38, wherein the subject is a human who is or has previously been treated with one or more TNF-α antagonists.

50. The method of claim 5, 6, 7, 8, 37 or 38, wherein the subject is a human who is not currently being treated with a TNF-α antagonist or methotrexate.

51. The method of claim 5, 6, 7, 8, 37 or 38, wherein the subject is a human with an inflammatory disorder that is refractory to treatment with a TNF-α antagonist, a non-steriodal anti-inflammatory agent or methotrexate alone.

52. The method of claim 2, 4, 6, 8 or 38, wherein VITAXIN.TM. or an antigen-binding fragment thereof is administered orally, topically, intravenously, intramuscularly or subcutaneously to said subject.

53. The method of claim 37 or 38, wherein MEDI-507 or an antigen-binding fragment thereof is administered orally, topically, intravenously, intramuscularly or subcutaneously to said subject.

54. The method of claim 1, 3, 5, 7 or 37, wherein said integrin $\alpha_v\beta_3$ antagonists are not small organic molecules.

55. The method of claim 1, 3, 5, 7 or 37, wherein at least one integrin $\alpha_v\beta_3$ antagonist is a small organic molecule.

56. The method of claim 7 or 8, wherein said CD2 binding molecules are not small organic molecules.

57. The method of claim 7 or 8, wherein at least one CD2 binding molecule is a small organic molecule.

58. A method of treating or ameliorating an inflammatory disorder or an autoimmune disorder or one or more symptoms thereof, said method comprising administering to a subject in need thereof a prophylactically or therapeutically effective amount of VITAXIN.TM. or an antigen-binding fragment thereof, a prophylactically or therapeutically effective amount of REMICADE.TM. or ENBREL.TM., and a prophylactically or therapeutically effective amount of methotrexate.

59. The method of claim 58, wherein the amount of VITAXIN.TM. or an antigen-binding fragment thereof administered to said subject is a dosage of about 0.1 mg/kg to 10 mg/kg.

60. The method of claim 58, wherein the amount of REMICADE.TM. administered to said subject is a dosage of about 0.1 mg/kg to 10 mg/kg.

61. The method of claim 58, wherein the amount of ENBREL.TM. administered to said subject is a dosage of about 0.01 mg/kg to 10 mg/kg.

62. The method of claim 58, wherein the methotrexate administered to said subject is a dosage of about 0.01 mg/kg to 3 mg/kg.

63. A pharmaceutical composition comprising an integrin $\alpha_v\beta_3$ antagonist, a TNF-α antagonist, and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising an integrin $\alpha_v\beta_3$ antagonist, a CD2 binding molecule, and a pharmaceutically acceptable carrier.

65. The composition of claim 63 further comprising methotrexate.

66. The composition of claim 63 or 65, wherein the integrin $\alpha_v\beta_3$ antagonist is VITAXIN.TM. or an antigen-binding fragment thereof.

67. The composition of claim 63, wherein the TNF-α antagonist is REMICADE.TM. or ENBREL.TM..

68. The composition of claim 64, wherein the CD2 binding molecule is LFA3TIP, MEDI-507, or antigen-binding fragment of MEDI-507.

69. A pharmaceutical composition comprising VITAXIN.TM. or an antigen-binding fragment thereof, MEDI-507 or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier.

70. An article of manufacture comprising packaging material and a pharmaceutical composition in suitable form for administration to a human contained within said packaging material, wherein said pharmaceutical composition comprises VITAXIN.TM. or an antigen-binding fragment thereof, MEDI-507 or an antigen-binding fragment thereof, a pharmaceutically acceptable carrier, and instructions contained with said packaging material which suggests a dosing regimen for the prevention or treatment of an inflammatory disorder or an autoimmune disorder.

L12 ANSWER 31 OF 38 USPATFULL on STN
2002:294292 Compositions and methods of monoclonal and polyclonal antibodies specific for T cell subpopulations.
Exley, Mark A., Chestnut Hill, MA, UNITED STATES
Wilson, Samuel B., Lexington, MA, UNITED STATES
Balk, Steven P., Needham, MA, UNITED STATES
US 2002164331 A1 20021107
APPLICATION: US 2001-885768 A1 20010619 (9)
PRIORITY: US 2000-212466P 20000619 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides compounds and methods for the ex vivo or in vivo expansion of NK T cells, CD1d-reactive T cells, and JαQ+ T cells, and the modulation of their activities. These compounds and methods have diagnostic and therapeutic applications.

CLM What is claimed is:

1. A purified antibody that preferentially binds a T cell antigen receptor (**TCR**), wherein said antibody preferentially binds a CDR3-loop or an α-β junction of said **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

2. The purified antibody of claim 1, that preferentially binds and preferentially expands an invariant T cell.

3. The purified antibody of claim 1, that preferentially binds the antigen binding site of the **TCR** of said T cell subpopulation.

4. A combination of purified antibodies that preferentially binds a **TCR**, wherein said antibody combination preferentially binds a CDR3-loop or an α-β junction of said **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; wherein said antibody combination is selected from the group consisting of: (i) an anti-Vα24 antibody and an anti-CD161 antibody; (ii) an anti-Vα24 antibody and an anti-CD94 antibody; (iii) an anti-**v**β11 antibody and an

anti-CD161 antibody, and (iv) an anti-Vβ11 antibody and an anti-CD94 antibody.

5. A fragment or derivative of an antibody, wherein said antibody preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

6. A bifunctional antibody comprising: (a) a first antibody or fragment thereof that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; wherein said first antibody or fragment binds a first epitope; and (b) a second antibody or fragment thereof that binds a second epitope expressed on a T cell expressing said **TCR** or expressed on a NK T cell, CD1d-reactive T cell, or JαQ+ T cell that is bound by said first antibody or fragment thereof.

7. A stable hybridoma that produces an antibody, wherein said antibody preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

8. A purified T cell subpopulation, wherein said T cells are specifically bound by an antibody or a combination of antibodies, wherein said antibody or said antibody combination preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or wherein said antibody preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

9. A method of generating an antibody that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said method comprising: (a) coupling a cyclic **peptide** to a carrier; (b) immunizing a mammal with said coupled **peptide**; and (c) isolating an antibody that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

10. A method of generating an antibody that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said method comprising: (a) immunizing a CD1 or invariant T cell deficient mammal with invariant T cells; and (b) isolating an antibody that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

11. The method of claim 9 or 10, wherein said mammal is a CD1d knockout mouse, a mammal tolerized to NK T cells, a mammal tolerized to CD1d-reactive T cells, a mammal tolerized to JαQ+ T cell, a mammal tolerized to the invariant **TCR**, a mammal in which invariant T cells have been removed, a mammal lacking part of the a chain of said

TCR a chain, or a mammal lacking part of the β chain of said **TCR**.

12. A method of measuring the amount of NK TCRs or the amount of NK T cells in a sample, said method comprising contacting said sample with an antibody that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs.

13. A method of measuring the amount of CD1d-reactive TCRs or the amount of CD1d-reactive T cells in a sample, said method comprising contacting said sample with an antibody that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs.

14. A method of measuring the amount of JαQ+ TCRs or the amount of JαQ+ T cells in a sample, said method comprising contacting said sample with an antibody or a combination of antibodies that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs.

15. A method of visualizing the NK TCRs or the NK T cells in a sample, said method comprising contacting said sample with an antibody that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs.

16. A method of visualizing the CD1d-reactive TCRs or the CD1d-reactive T cells in a sample, said method comprising contacting said sample with an antibody that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs.

17. A method of visualizing the JαQ+ TCRs or the JαQ+ T cells in a sample, said method comprising contacting said sample with an antibody or a combination of antibodies that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs.

18. A method of diagnosing a subject with a condition or an increased risk for a condition selected from the group consisting of autoimmune disease, viral infection, bacterial infection, parasitic infection, infection by a eukaryotic pathogen, allergy, asthma, inflammatory condition, graft versus host disease, graft rejection, immunodeficiency disease, spontaneous abortion, pregnancy, and cancer; said method comprising the following: (a) contacting a sample from said subject with an antibody or a combination of antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or an antibody that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; (b) quantitating the amount of said antibody or said antibody combination bound to said **TCR** or said T cells; thereby determining the amount of T cells of interest in said sample; and (c) comparing the amount of said T cells of interest in said sample to the amount of said T cells of interest found in subjects diagnosed with said condition or subjects not diagnosed with said condition.

19. The method of claim 18, further comprising comparing the amount of another T cell type in said sample with the amount of said another T cell type found in subjects diagnosed with said condition or subjects not diagnosed with said condition.

20. A method of treating or preventing an autoimmune disease, viral infection, bacterial infection, parasitic infection, infection by a eukaryotic pathogen, allergy, asthma, inflammatory condition, graft versus host disease, graft rejection, immunodeficiency disease, spontaneous abortion, pregnancy, or cancer in a mammal, said method comprising administering to said mammal an antibody or a combination of

antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

21. A method of inhibiting T cell pathogenesis in a mammal, said method comprising administering to said mammal an antibody or a combination of antibodies that preferentially binds a CDR3-loop, an antigen binding site, or an α-β junction of said TCRs; or inhibits the expansion of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said administering sufficient to inhibit a T cell expressing said **TCR**, a NIK T cell, a CD1d-reactive T cell, or a JαQ+ T cell.

22. The method of claim 21, wherein said antibody is covalently linked to a toxin or a radiolabel.

23. A method of increasing the size of a subpopulation of T cells, said method comprising contacting a sample comprising said T cells with an antibody that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, JαQ+ T cells, and T cells expressing a CDR3-loop or an α-β junction of a **TCR** that is preferentially bound by said antibody, wherein said contacting occurs under conditions that result in an increase in the number of said T cells.

24. The method of claim 23, further comprising contacting said sample with an antigen and antigen presenting cells under conditions that allow said contacting to increase the number of said T cells; wherein said antigen is not α-galactosylceramide.

25. The method of claim 24, wherein said antigen is a lipid or glycosyl-phosphatidylinositol antigen from an infectious pathogen, an antigen from a cancerous cell, or a self-lipid.

26. The method of claim 23, further comprising contacting said sample with an antigen and antigen presenting cells under conditions that allow said contacting to increase the number of said T cells; wherein said antigen is α-galactosylceramide.

27. A method of increasing the size of a subpopulation of T cells, said method comprising: (a) contacting a sample comprising said T cells with an antibody or a combination of antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or an antibody that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said contacting conducted under conditions that allow complex formation between said T cells and said antibody or said combination of antibodies; (b) isolating said complex; and (c) contacting said T cells in said complex or recovered from said complex with an antigen and antigen presenting cells under conditions that allow said contacting to increase the number of said T cells; wherein said antigen is not α-galactosylceramide.

28. The method of claim 27, wherein said antigen is a lipid or glycosyl-phosphatidylinositol antigen from an infectious pathogen, an antigen from a cancerous cell, or a self-lipid.

29. A method of increasing the size of a subpopulation of T cells, said method comprising: (a) contacting a sample comprising said T cells with an antibody or a combination of antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or an antibody that preferentially binds or modulates the expansion or activation of at

least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said contacting conducted under conditions that allow complex formation between said T cells and said antibody or said combination of antibodies; (b) isolating said complex; and (c) contacting said T cells in said complex or recovered from said complex with an antigen and antigen presenting cells under conditions that allow said contacting to increase the number of said T cells; wherein said antigen is wherein said antigen is α-galactosylceramide.

30. The method of claim 27 or 29, further comprising contacting said sample or said complex with one or more cytokines.

31. A method of increasing the size of a subpopulation of T cells in a mammal, said method comprising: (a) obtaining a sample comprising said T cells from said mammal; (b) contacting said T cells with an antibody or a combination of antibodies that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, JαQ+ T cells, and T cells expressing a CDR3-loop or an α-β junction of a **TCR** that is preferentially bound by said antibody or said antibody combination; said contacting conducted under conditions that allow said contacting to increase the number of said T cells; and (c) administering said contacted T cells to said mammal.

32. The method of claim 31, further comprising purifying said T cells prior to said contacting step or after said contacting step.

33. A method of increasing the size of a subpopulation of T cells in a mammal, said method comprising: (a) obtaining a sample comprising said T cells from said mammal; (b) contacting said T cells with an antibody or a combination of antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or an antibody that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said contacting conducted under conditions that allow complex formation between said T cells and said antibody or said combination of antibodies; (c) isolating said complex; and (d) contacting said T cells in said complex or recovered from said complex with an antigen and antigen presenting cells under conditions that allow said contacting to increase the number of said T cells; wherein said antigen is not α-galactosylceramide; and (e) administering said contacted T cells to said mammal.

34. The method of claim 33, wherein said antigen is a lipid or glycosyl-phosphatidylinositol antigen from an infectious pathogen, an antigen from a cancerous cell, or a self-lipid.

35. A method of increasing the size of a subpopulation of T cells in a mammal, said method comprising: (a) obtaining a sample comprising said T cells from said mammal; (b) contacting said T cells with an antibody or a combination of antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or an antibody that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells; said contacting conducted under conditions that allow complex formation between said T cells and said antibody or said combination of antibodies; (c) isolating said complex; and (d) contacting said T cells in said complex or recovered from said complex with an antigen and antigen presenting cells under conditions that allow said contacting to increase the number of said T cells; wherein said antigen is α-galactosylceramide; and (e) administering said contacted T cells to said mammal.

36. The method of claim 33 or 35, further comprising administering one

T cells. This motif is associated with autoimmune diseases, such as multiple sclerosis (MS). Once the motif is detected, the autoimmune disease can be treated or its progress monitored. The autoimmune disease can be treated by administering a **peptide** comprising the LGRAGLTY motif.

CLM What is claimed is:

1. An oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1.

2. The oligonucleotide of claim 1, which comprises at least 15 contiguous nucleotides of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1.

3. The oligonucleotide of claim 1, which comprises the sequence of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1.

4. A primer pair, comprising: (a) a first primer of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO:1, or the nucleic acid complementary thereto; and (b) a second primer comprising a nucleic acid of about 15 and 30 nucleotides in length that does not comprise the sequence of (a) and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **T cell receptor** T cells, wherein the sequences of said first and second primers are not found on the same strand of the **T cell receptor** gene.

5. The primer pair of claim 4, wherein the second primer comprises SEQ ID NO:2.

6. An oligonucleotide probe comprising: (a) an oligonucleotide of about 10 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1 and (b) a labeling moiety.

7. The oligonucleotide probe of claim 6, wherein the labeling moiety is selected from ^{32} P or digoxingenin.

8. A method of detecting MBP83-99 **V**β13.1 T cells expressing a **T cell receptor** LGRAGLTY motif, comprising: (a) obtaining a nucleic acid sample from MBP83-99 **V**β13.1 T cells; (b) contacting the nucleic acid sample with a primer pair selected from: (i) a first oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1; and (ii) a second oligonucleotide of about 15 and 30 nucleotides in length that does not comprise the sequence of the first oligonucleotide and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **T cell receptor** T cells, wherein the sequences of the first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene; and (c) detecting the presence of the nucleic acid encoding the LGRAGLTY motif.

9. The method of claim 8, wherein the second primer comprises SEQ ID NO:2.

10. The method according to claim 8, wherein a fragment of the nucleic acid sample is amplified by polymerase chain reaction (PCR).

11. The method according to claim 10, wherein the detection step comprises probing with an oligonucleotide probe comprising: (a) an oligonucleotide, which comprises the sequence of SEQ ID NO:1, or the nucleic acid complementary thereto; and, (b) a labeling moiety.

12. The method according to claim 10, wherein the detection step comprises autoradiography.

13. A test kit comprising a first oligonucleotide of about 15-30 nucleotides in length: said first oligonucleotide comprising at least 10 contiguous nucleotides of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1.

14. The test kit of claim 13, further comprising: a second oligonucleotide of about 15 and 30 nucleotides in length that does not comprise the sequence of said first oligonucleotide and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **T cell receptor** T cells, wherein the sequences of the first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene.

15. The test kit of claim 14, wherein the second primer comprises SEQ ID NO:2.

16. The test kit of claim 13, further comprising a labeling moiety, wherein the labeling moiety is selected from ^{32}P or digoxingenin.

17. A method of monitoring an autoimmune disease, comprising: (A) obtaining MBP83-99 **V**β13.1 T cells from a human; (B) detecting the presence of a nucleic acid encoding a LGRAGLTY motif by (i) obtaining a nucleic acid sample from MBP83-99 **V**β13.1 T cells; (ii) contacting the nucleic acid sample with a primer pair selected from: (a) a first oligonucleotide of about 15 to 30 nucleotides in length, comprising at least 10 contiguous nucleotides of SEQ ID NO:1, or comprising at least 10 contiguous nucleotides of the complement of SEQ ID NO:1; and (b) a second oligonucleotide of about 15 and 30 nucleotides in length that does not comprise the sequence of said first oligonucleotide and is found in the region from **V**β to Jβ of the **V**β13.1 gene in **T cell receptor** T cells, wherein the sequences of said first and second oligonucleotides are not found on the same strand of the **T cell receptor** gene; and (c) detecting the presence of the nucleic acid encoding the LGRAGLTY motif; and, if the nucleic acid is detected, (C) quantifying the amount of the nucleic acid.

18. The method of 17, wherein the second primer comprises SEQ ID NO:2.

L12 ANSWER 35 OF 38 USPATFULL on STN
2001:125558 Recombinant MHC molecules useful for manipulation of antigen-specific T-cells.
Burrows, Gregory G., Portland, OR, United States
Vandenbark, Arthur A., Portland, OR, United States
Oregon Health Sciences University, Portland, OR, United States (U.S. corporation)
US 6270772 B1 20010807
APPLICATION: US 1998-153586 19980915 (9)
PRIORITY: US 1997-64552P 19970916 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Two-domain MHC **polypeptides** useful for manipulation of antigen-specific T-cells are disclosed. These **polypeptides** include MHC class II-based molecules that comprise covalently linked β1 and α1 domains, and MHC class I-based molecules that comprise covalently linked α1 and α2 domains. These **polypeptides** may also include covalently linked antigenic determinants, toxic moieties, and/or detectable labels. The disclosed **polypeptides** can be used to target antigen-specific T-cells, and are useful, among other things, to detect and purify antigen-specific T-cells, to induce or activate T-cells, and to treat conditions mediated by antigen-specific

T cells.

CLM What is claimed is:

1. A purified MHC Class II **polypeptide** comprising covalently linked first and second domains, wherein: the first domain is a mammalian MHC class II β1 domain and the second domain is a mammalian MHC class II α1 domain and wherein the amino terminus of the second domain is covalently linked to the carboxy terminus of the first domain and wherein the MHC class II molecule does not include an α2 or a β2 domain.

2. The **polypeptide** of claim 1 wherein the covalent linkage between the first and second domains is provided by a **peptide** linker sequence.

3. The **polypeptide** of claim 1 wherein the **polypeptide** further comprises, covalently linked to the amino terminus of the first domain, a third domain comprising an antigenic determinant.

4. The **polypeptide** of claim 3 wherein the antigenic determinant is a **peptide** antigen.

5. The **polypeptide** of claim 4 wherein the covalent linkage between the first and third domains is provided by a **peptide** linker sequence.

6. The **polypeptide** of claim 1 further comprising an antigenic determinant associated with the **polypeptide** by non-covalent interaction.

7. The **polypeptide** of claim 6 wherein the antigenic determinant is a **peptide** antigen.

8. The **polypeptide** of claim 1 wherein the **polypeptide** further comprises a covalently linked detectable marker or toxic moiety.

9. A pharmaceutical composition comprising a **polypeptide** according to claim 1 and a pharmaceutically acceptable carrier.

10. A recombinant **polypeptide** comprising α1 and β1 domains of a mammalian MHC class II molecule wherein the amino terminus of the α1 domain is covalently linked to the carboxy terminus of the β1 domain, and wherein the MHC class II molecule does not include either an α2 domain or a β2 domain.

11. The recombinant **polypeptide** according to claim 10, wherein the **polypeptide** further comprises an antigenic determinant associated with the **polypeptide** by covalent or non-covalent interaction.

12. The recombinant **polypeptide** according to claim 11 wherein the antigenic determinant is covalently linked to the amino terminus of the β1 domain.

13. The recombinant **polypeptide** according to claim 10 wherein the **polypeptide** further comprises a detectable marker or toxic moiety.

14. The purified MHC **polypeptide** of claim 10, wherein the MHC **polypeptide** is non-covalently associated with an antigen.

15. A recombinant **polypeptide** comprising only two domains of an MHC class II **peptide**, wherein the two domains are an α1 domain and a β1 domain, wherein the amino terminus of the α1 domain is covalently linked to the carboxy terminus of the β1 domain.

16. The purified MHC **polypeptide** of claim 15, wherein the MHC **polypeptide** is covalently associated with an antigen.

17. The purified MHC **polypeptide** of claim 15, wherein the MHC

polypeptide is non covalently associated with an antigen.

18. The **polypeptide** of claim 10 or 15, wherein the covalent linkage between the α1 and β1 domains is provided by a **peptide** linker sequence.

L12 ANSWER 36 OF 38 USPATFULL on STN
2001:97421 Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein.
Gaur, Amitabh, San Diego, CA, United States
Conlon, Paul, Solana Beach, CA, United States
Ling, Nicholas C., San Diego, CA, United States
Staehelin, Theophil, Arlesheim, Switzerland
Crowe, Paul D., Encinitas, CA, United States
Neurocrine Biosciences, Inc., San Diego, CA, United States (U.S. corporation)Novartis AG, Basel, Switzerland (non-U.S. corporation)
US 6251396 B1 20010626
APPLICATION: US 1998-137759 19980820 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed toward **peptide** analogs of human myelin basic protein. The **peptide** analog is at least seven amino acids long and derived from residues 83 to 99 of human myelin basic protein. The analogs are altered from the native sequence at least at positions 91, 95, or 97. Additional alterations may be made at other positions. Pharmaceutical compositions containing these **peptide** analogs are provided. The **peptide** analogs are useful for treating multiple sclerosis.
CLM What is claimed is:
1. A method for inducing a **Th2** immune response to myelin basic protein or a **peptide** analog thereof in a patient, comprising: administering to a patient a composition comprising a **peptide** analog comprising contiguous residues 83-99 of human myelin basic protein, wherein the L-glutamic acid at position 83 is altered to D-alanine, L-asparagine at position 84 is altered to L-lysine, L-phenylalanine at position 89 is altered to L-leucine, and L-lysine at position 91 is altered to L-alanine, wherein the **peptide** analog is administered in combination with a physiologically acceptable carrier or diluent.

2. The method of claim 1, wherein the composition further comprises an adjuvant.

3. The method of claim 2, wherein the adjuvant is alum.

L12 ANSWER 37 OF 38 USPATFULL on STN
1999:106440 Methods for treatment of multiple sclerosis utilizing **peptide** analogues of human myelin basic protein.
Gaur, Amitabh, San Diego, CA, United States
Conlon, Paul J., Solana Beach, CA, United States
Ling, Nicholas, San Diego, CA, United States
Neurocrine Biosciences, Inc., San Diego, CA, United States (U.S. corporation)
US 5948764 19990907
APPLICATION: US 1997-781122 19970109 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed toward **peptide** analogues of human myelin basic protein for use in the treatment of multiple sclerosis. Within one aspect, **peptide** analogues suitable for treating multiple sclerosis are provided which are at least seven amino acids long and derived from residues 86 to 99 of human myelin basic protein. In addition, such analogues may be altered from the native sequence at positions 87, 88, 97, 98 or 99 to a D-amino acid. Additional alterations may be made at other positions. Pharmaceutical compositions containing

these **peptide** analogues are also provided, as well as methods for treating multiple sclerosis.

CLM What is claimed is:

1. A **peptide** analogue comprising at least seven consecutive amino acids selected from residues 86 to 99 of human myelin basic protein, including residue 97, wherein the L-arginine at position 97 is altered to a D-amino acid, said **peptide** analogue having increased MHC binding relative to MBP 87-99.

2. The **peptide** analogue of claim 1 wherein the L-arginine at position 97 is altered to D-alanine.

3. The **peptide** analogue of claim 1 wherein the L-arginine at position 97 is altered to a D-amino acid selected from the group consisting of D-arginine, D-asparagine, D-aspartic acid, D-cysteine, D-glutamine, D-glutamic acid, D-glycine, D-histidine, D-isoleucine, D-leucine, D-lysine, D-methionine, D-phenylalanine, D-proline, D-serine, D-threonine, D-tryptophan, D-tyrosine and D-valine.

4. The **peptide** analogue according to claim 1 wherein the N-terminal and/or C-terminal amino acids are altered to a D-amino acid, such that upon administration of the **peptide** analogue in vivo proteolysis is reduced.

5. A **peptide** analogue comprising at least seven consecutive amino acids selected from residues 86 to 99 of human myelin basic protein, including residue 97, wherein the L-arginine at position 97 is altered to L-alanine.

6. A composition comprising a **peptide** analogue according to any one of claims 1-4 or 5, in combination with a pharmaceutically acceptable carrier or diluent.

L12 ANSWER 38 OF 38 USPATFULL on STN

1999:96351 DNA vaccination for induction of suppressive T cell response.

Steinman, Lawrence, Palo Alto, CA, United States
Waisman, Ari, Tel-Aviv, Israel
The Board of Trustees of The Leland Stanford Junior University, Palo Alto, CA, United States (U.S. corporation)
US 5939400 19990817
APPLICATION: US 1996-606639 19960226 (8)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A pro-inflammatory T response is specifically prevented by the injection into a recipient of DNA encoding the variable region of a **T cell receptor**. In response to the vaccination, T cells expressing the variable region produce **Th2** cytokines, including IL-4. A pro-inflammatory T cell response directed to an autoantigen is shown to be suppressed by DNA vaccination. The suppressive vaccination further reduced the inflammatory effect of T cells reactive against epitopes of the autoantigen not recognized by the variable region used for vaccination.

CLM What is claimed is:

1. A method of suppressing **Th1** type T cell response in a myelin basic protein associated autoimmune disease, the method comprising: injecting into muscle tissue of a mammalian host a DNA expression vector comprising: a sequence encoding the variable region of a **T cell receptor** that (a) is selected from the group consisting of mouse **V**β8.2, mouse **V**β17a, human **V**β5, human **V**β6, human **V**β4 subfamily and human **V**β12 subfamily, (b) recognizes an epitope of myelin basic protein, and (c) is under the regulatory control of a promoter that is active in said muscle tissue, wherein said expression cassette is incorporated into muscle cells of said host and said sequence is expressed at levels sufficient to suppress said **Th1** type T cell response, and wherein said

suppression of the **TH1** type 1 cell response prevents onset of said myelin basic protein associated autoimmune disease.

2. A method according to claim 1, further comprising the step of injecting cardiotoxin into said muscle tissue, prior to said introducing step.

3. A method according to claim 1, wherein said DNA expression vector is a plasmid.

4. A method according to claim 3, wherein said plasmid is transiently expressed in said muscle cells.

5. A method according to claim 1, wherein said mammalian host is a mouse and wherein said sequence encoding the variable region of a **T cell receptor** is mouse **V**β8.2.

6. A method according to claim 1, wherein said autoimmune disease is multiple sclerosis.

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=> d his

     (FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

     FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
                E MARCHALONIS JOHN J/IN
L1             2 S E3

     FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
                E MARCHALONIS J J/IN
L2             5 S E2 OR E3

     FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
                E MARCHALONIS J J/AU
L3           256 S E2-E5
L4            75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5             4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6             0 S L4 AND (TH1 (W) TH2)

     FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7          9668 S (TCR OR T-CELL RECEPTOR)
L8          7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9           816 S L8 AND (V BETA)
L10          123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11           39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12           38 S L11 NOT L1

=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              115.68     167.81

FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004

 FILE LAST UPDATED: 4 MAR 2004 (20040304/UP).  FILE COVERS 1953 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.
```

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s (T cell receptor or TCR)
       3600566 T
       1750104 CELL
        449346 RECEPTOR
         15796 T CELL RECEPTOR
                 (T(W)CELL(W)RECEPTOR)
         16179 TCR
L13      24107 (T CELL RECEPTOR OR TCR)

=> s l13 and (TH1 or TH2 or T-helper 1 or T-helper 2)
         12397 TH1
         11454 TH2
       3600566 T
         26901 HELPER
       3176810 1
          1108 T-HELPER 1
                 (T(W)HELPER(W)1)
       3600566 T
         26901 HELPER
       2769753 2
           817 T-HELPER 2
                 (T(W)HELPER(W)2)
L14       1326 L13 AND (TH1 OR TH2 OR T-HELPER 1 OR T-HELPER 2)

=> s l14 and (altered peptide ligands)
        142721 ALTERED
        261675 PEPTIDE
         63277 LIGANDS
           160 ALTERED PEPTIDE LIGANDS
                 (ALTERED(W)PEPTIDE(W)LIGANDS)
L15         18 L14 AND (ALTERED PEPTIDE LIGANDS)

=> d l15,ti,1-18

L15  ANSWER 1 OF 18     MEDLINE on STN
TI   Hierarchical signaling thresholds determine the fates of naive T cells:
     partial priming leads nai;ve T cells to unresponsiveness.

L15  ANSWER 2 OF 18     MEDLINE on STN
TI   CD2 facilitates differentiation of CD4 Th cells without affecting
     Th1/Th2 polarization.

L15  ANSWER 3 OF 18     MEDLINE on STN
TI   The balance of protein kinase C and calcium signaling directs T cell
     subset development.

L15  ANSWER 4 OF 18     MEDLINE on STN
TI   Th1 and Th2 deviation of myelin-autoreactive T cells by altered
     peptide ligands is associated with reciprocal regulation of Lck, Fyn,
     and ZAP-70.

L15  ANSWER 5 OF 18     MEDLINE on STN
TI   Antigen-specific signaling by a soluble, dimeric peptide/major
     histocompatibility complex class II/Fc chimera leading to T helper cell
     type 2 differentiation.

L15  ANSWER 6 OF 18     MEDLINE on STN
TI   Cross-reactivity of T-cell clones specific for altered peptide
     ligands of myelin basic protein.

L15  ANSWER 7 OF 18     MEDLINE on STN
TI   Altered ligands reveal limited plasticity in the T cell response to a
     pathogenic epitope.
```

L15 ANSWER 8 OF 18 MEDLINE on STN
TI **TCR**-independent pathways mediate the effects of antigen dose and **altered peptide ligands** on Th cell polarization.

L15 ANSWER 9 OF 18 MEDLINE on STN
TI An altered peptide ligand specifically inhibits **Th2** cytokine synthesis by abrogating **TCR** signaling.

L15 ANSWER 10 OF 18 MEDLINE on STN
TI Differential effects of CD28 engagement and IL-12 on T cell activation by **altered peptide ligands**.

L15 ANSWER 11 OF 18 MEDLINE on STN
TI **Altered peptide ligands** of islet autoantigen Imogen 38 inhibit antigen specific T cell reactivity in human type-1 diabetes.

L15 ANSWER 12 OF 18 MEDLINE on STN
TI Inhibition of an in vitro CD4+ T cell alloresponse using **altered peptide ligands**.

L15 ANSWER 13 OF 18 MEDLINE on STN
TI Changes in cytokine secretion induced by **altered peptide ligands** of myelin basic protein peptide 85-99.

L15 ANSWER 14 OF 18 MEDLINE on STN
TI Induction of IL-4-producing CD4+ T cells by antigenic peptides altered for **TCR** binding.

L15 ANSWER 15 OF 18 MEDLINE on STN
TI Response of a human T cell clone to a large panel of **altered peptide ligands** carrying single residue substitutions in an antigenic peptide: characterization and frequencies of **TCR** agonism and **TCR** antagonism with or without partial activation.

L15 ANSWER 16 OF 18 MEDLINE on STN
TI Signalling events in the anergy induction of **T helper 1** cells.

L15 ANSWER 17 OF 18 MEDLINE on STN
TI **Altered peptide ligands** can control CD4 T lymphocyte differentiation in vivo.

L15 ANSWER 18 OF 18 MEDLINE on STN
TI Separation of **T helper 1** clone cytolysis from proliferation and lymphokine production using analog peptides.

=> d l15,cbib,ab,1,2,8,9,15

L15 ANSWER 1 OF 18 MEDLINE on STN
2002674951. PubMed ID: 12435401. Hierarchical signaling thresholds determine the fates of naive T cells: partial priming leads nai;ve T cells to unresponsiveness. Yamashiro Hiromichi; Odani Yo; Hozumi Nobumichi; Nakano Naoko. (Research Institute for Biological Sciences, Science University of Tokyo, 2669 Yamazaki, Noda City, 278-0022, Chiba, Japan.) Biochemical and biophysical research communications, (2002 Nov 22) 299 (1) 148-54. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB Differing conditions of antigen priming varying either the concentration or affinity of **T cell receptor** (**TCR**) ligands greatly alter T cell responses. Here, we demonstrate that antigen-specific CD4(+) nai;ve T cells primed with either **altered peptide ligands** (APLs) or a minimal concentration of antigen peptide become anergic without observable cell divisions. Transforming growth factor-beta1 (TGF-beta1) expression was induced 24h following in these stimulation conditions producing anergic cells. Productively stimulated nai;ve T cells expressed IL-2 to

differentiate into **T helper 1** (Th1) cells, secreting interferon-gamma (IFN-gamma) upon secondary antigen stimulation; T cells primed with an APL did not secrete either interleukin-4 (IL-4) or IFN-gamma, but expressed TGF-beta1 and Tob, a member of the anti-proliferative gene family. Therefore, T cell responses are regulated by **TCR** signaling depending on the extent of **TCR** engagement. These results suggest that partial antigen stimulation in the periphery can induce nai;ve CD4(+)T cell unresponsiveness.

L15 ANSWER 2 OF 18 MEDLINE on STN

2002075941. PubMed ID: 11801645. CD2 facilitates differentiation of CD4 Th cells without affecting **Th1/Th2** polarization. Sasada Tetsuro; Yang Hailin; Reinherz Ellis L. (Laboratory of Immunobiology, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, USA.) Journal of immunology (Baltimore, Md. : 1950), (2002 Feb 1) 168 (3) 1113-22. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The role of CD2 in murine CD4 helper T cell differentiation and polarization was examined using **TCR**-Cyt-5CC7-I transgenic recombination activating gene-2-/- H-2(a) mice on CD2+/+ or CD2-/- backgrounds. In the absence of CD2, thymic development was abnormal as judged by reduction in the steady state number of total, double-positive, and CD4 single-positive (SP) thymocytes, as well as a defect in their restorative dynamics after peptide-induced negative selection in vivo. In addition, in CD2-/- animals, lymph node CD4 SP T cells manifest a 10- to 100-fold attenuated activation response to cytochrome c (CytC) agonist peptides as judged by induction of CD25 and CD69 cell surface expression or [(3)H]TdR incorporation; differences in the magnitude of responsiveness and requisite molar peptide concentrations were even greater for **altered peptide ligands**. Although the presence or absence of CD2 did not impact the final **Th1** or **Th2** polarization outcome, CD2 expression reduced the CytC peptide concentration threshold necessary to facilitate both **Th1** and **Th2** differentiation. In vivo administration of CytC peptide to CD2-/- animals yielded an impaired CD4 SP T cell effector/memory phenotype compared with similarly treated CD2+/+ mice. Analysis of **TCR**-Cyt-5CC7-I human CD2 double-transgenic mice similarly failed to reveal a preferential **Th1** vs **Th2** polarization. Collectively, these results indicate that CD2 is important for the efficient development of CD4 SP thymocytes and **TCR**-dependent activation of mature CD4 lymph node T cells, but does not direct a particular helper T cell subset polarity.

L15 ANSWER 8 OF 18 MEDLINE on STN

1999138883. PubMed ID: 9973460. **TCR**-independent pathways mediate the effects of antigen dose and **altered peptide ligands** on Th cell polarization. Grakoui A; Donermeyer D L; Kanagawa O; Murphy K M; Allen P M. (Center for Immunology and Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110, USA.) Journal of immunology (Baltimore, Md. : 1950), (1999 Feb 15) 162 (4) 1923-30. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We examined the role of the peptide/MHC ligand in CD4+ T cell differentiation into **Th1** or **Th2** cells using a **TCR** alphabeta transgenic mouse specific for hemoglobin (Hb)(64-76)/I-Ek. We identified two **altered peptide ligands** of Hb(64-76) that retain strong agonist activity but, at a given dose, induce cytokine patterns distinct from the Hb(64-76) peptide. The ability of these peptides to produce distinct cytokine patterns at identical doses is not due to an intrinsic qualitative property. Each peptide can induce **Th2** cytokines at low concentrations and **Th1** cytokines at high concentrations and has a unique range of concentrations at which these distinct effects occur. The pattern of cytokines produced from limiting dilution of naive T cells demonstrated that the potential to develop an individual **Th1** or **Th2** cell is stochastic, independent of Ag dose. We propose that the basis for the observed effects on the **Th1/Th2** balance shown by the **altered peptide ligands** and the amount of Ag dose involves the modification of

soluble factors in bulk cultures that are the driving force that polarize the population to either a **Th1** or **Th2** phenotype.

L15 ANSWER 9 OF 18 MEDLINE on STN

1999138872. PubMed ID: 9973449. An altered peptide ligand specifically inhibits **Th2** cytokine synthesis by abrogating **TCR** signaling. Faith A; Akdis C A; Akdis M; Joss A; Wymann D; Blaser K. (Swiss Institute of Allergy and Asthma Research, Davos, Switzerland.. siaf@siaf.unizh.ch) . Journal of immunology (Baltimore, Md. : 1950), (1999 Feb 1) 162 (3) 1836-42. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **Altered peptide ligands** (APL) can modify T cell effector function by their diversity in binding to the **TCR** or MHC class II-presenting molecules. The capacity to inhibit **Th2** cytokine production by allergen-specific T cells would contribute to combating allergic inflammation. The presence of APL generated by Ala-substitutions in a synthetic dodeca-peptide spanning an immunodominant epitope of bee venom phospholipase A2 (PLA) was investigated in human T cells. Four of five substituted peptides reduced proliferation, IL-4, and IFN-gamma production by cloned PLA-specific Th0 cells proportionately. However, one APL, PLA-F82A, inhibited IL-4 but had no effect on IFN-gamma production. This uncoupling of IL-4 from IFN-gamma production was also observed on immunogenic restimulation of the cloned T cells pre-exposed to the APL/APCs. It appeared to result from lower affinity of binding to MHC class II by the APL compared with the native peptide. The APL also inhibited IL-4 production by polyclonal T cells. In consequence of the change in cytokine secretion, the production of IgG4 in vitro increased by PLA-F82A stimulation, compared with the native peptide. Exposure of the cloned T cells to either the APL or the native peptide, in the absence of professional APC, induced anergy such that proliferation and production of IL-4, IL-5, and IL-13 was abrogated on immunogenic rechallenge. Defective T cell activation appeared to result from alterations in transmembrane signaling through the **TCR**, specifically to lack of tyrosine phosphorylation of the tyrosine kinase, ZAP-70.

L15 ANSWER 15 OF 18 MEDLINE on STN

97047765. PubMed ID: 8892606. Response of a human T cell clone to a large panel of **altered peptide ligands** carrying single residue substitutions in an antigenic peptide: characterization and frequencies of **TCR** agonism and **TCR** antagonism with or without partial activation. Chen Y Z; Matsushita S; Nishimura Y. (Department of Neuroscience and Immunology, Kumamoto University Graduate School of Medical Sciences, Japan.) Journal of immunology (Baltimore, Md. : 1950), (1996 Nov 1) 157 (9) 3783-90. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB A CD4+ human T cell clone YN5-32 recognized a streptococcal M12p54-68 peptide in the context of HLA-DR4 and produced a large amount of IFN-gamma. We investigated responses of YN5-32 to 156 independent analogue peptides carrying single residue substitutions at residues 57 (position 1 (p1)) to 65 (p9) of the peptide. Approximately 30% of analogues at either Leu57 (p1), Ala60 (p4), or Asn62 (p6) residues exhibited **TCR** agonism to stimulate various magnitudes of proliferative responses in the T cell clone, and analogues exhibiting **TCR** antagonism are rare in these three residues. In analogues at either Glu58 (p2), Gln59 (p3), Tyr61 (p5), or Glu63 (p7) residue, 30 to 50% exhibited **TCR** antagonism. About 10% of analogues at Glu58 (p2) or Tyr61 (p5) stimulated proliferative responses, while 30 to 50% of analogues at Gln59 (p3) or Glu63 (p7) did so. Some of these **TCR** antagonistic analogues carrying relatively conservative amino acid substitutions partially activated the T cells to induce large increases in size and expression levels of CD4, CD11a (LFA-1), CD28, CD49d (VLA-4), and CD95 (Fas), and small increases in CD25 and CD44 expressions on the cell surface. None of the partially activating antagonistic analogues induced IFN-gamma production or anergy in T cells. Analogues with replacements of acidic amino acids at either Leu64 (p8) or Ser65 (p9) residue had dominant negative effects on T cell proliferation. Thus, **altered peptide ligands** with single residue

substitutions in the antigenic peptide frequently stimulated the human T cell clone, in at least three different ways to exhibit agonism, antagonism, and antagonism with partial activation. Frequencies of analogue peptides exhibiting these three different effects on the T cell clone differed depending on the residue of the peptide substituted. Altered T cell responses induced by analogue peptides of a T cell epitope provide a system to analyze activation signals mediated by **TCR**, and to manipulate T cell responses.

```
=> d his

     (FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

     FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
                E MARCHALONIS JOHN J/IN
L1              2 S E3

     FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
                E MARCHALONIS J J/IN
L2              5 S E2 OR E3

     FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
                E MARCHALONIS J J/AU
L3            256 S E2-E5
L4             75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5              4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6              0 S L4 AND (TH1 (W) TH2)

     FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7           9668 S (TCR OR T-CELL RECEPTOR)
L8           7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9            816 S L8 AND (V BETA)
L10           123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11            39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12            38 S L11 NOT L1

     FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004
L13         24107 S (T CELL RECEPTOR OR TCR)
L14          1326 S L13 AND (TH1 OR TH2 OR T-HELPER 1 OR T-HELPER 2)
L15            18 S L14 AND (ALTERED PEPTIDE LIGANDS)

=> e evavold b d/au
E1              3     EVAUL J E/AU
E2              6     EVAVOLD B/AU
E3             21 --> EVAVOLD B D/AU
E4              6     EVAVOLD BRIAN D/AU
E5              2     EVAVOLD E R/AU
E6              1     EVBUOMA N/AU
E7             14     EVBUOMWAN I/AU
E8              4     EVBUOMWAN I O/AU
E9              1     EVBUOMWAN L/AU
E10             2     EVBUOMWAN M I/AU
E11             1     EVCEB EVA A I/AU
E12             1     EVCEEVA T A/AU

=> s e2-e4
              6 "EVAVOLD B"/AU
             21 "EVAVOLD B D"/AU
              6 "EVAVOLD BRIAN D"/AU
L16          33 ("EVAVOLD B"/AU OR "EVAVOLD B D"/AU OR "EVAVOLD BRIAN D"/AU)

=> d l16,ti,1-33

L16  ANSWER 1 OF 33     MEDLINE on STN
TI   An MHC anchor-substituted analog of myelin oligodendrocyte glycoprotein
```

33 33 induces IFN gamma and autoantibodies in the absence of experimental autoimmune encephalomyelitis and optic neuritis.

L16 ANSWER 2 OF 33 MEDLINE on STN
TI CD43 modulates severity and onset of experimental autoimmune encephalomyelitis.

L16 ANSWER 3 OF 33 MEDLINE on STN
TI Regulation of polyclonal T cell responses by an MHC anchor-substituted variant of myelin oligodendrocyte glycoprotein 35-55.

L16 ANSWER 4 OF 33 MEDLINE on STN
TI Cutting edge: dependence of TCR antagonism on Src homology 2 domain-containing protein tyrosine phosphatase activity.

L16 ANSWER 5 OF 33 MEDLINE on STN
TI TCR reserve: a novel principle of CD4 T cell activation by weak ligands.

L16 ANSWER 6 OF 33 MEDLINE on STN
TI Dissociation of peripheral T cell responses from thymocyte negative selection by weak agonists supports a spare receptor model of T cell activation.

L16 ANSWER 7 OF 33 MEDLINE on STN
TI Antimicrobial properties of porphyrins.

L16 ANSWER 8 OF 33 MEDLINE on STN
TI DO11.10 and OT-II T cells recognize a C-terminal ovalbumin 323-339 epitope.

L16 ANSWER 9 OF 33 MEDLINE on STN
TI Cutting edge: dueling TCRs: peptide antagonism of CD4+ T cells with dual antigen specificities.

L16 ANSWER 10 OF 33 MEDLINE on STN
TI Conserved T cell receptor repertoire in primary and memory CD8 T cell responses to an acute viral infection.

L16 ANSWER 11 OF 33 MEDLINE on STN
TI Persistence of peptide-induced CD4+ T cell anergy in vitro.

L16 ANSWER 12 OF 33 MEDLINE on STN
TI Enhanced dissociation of HLA-DR-bound peptides in the presence of HLA-DM.

L16 ANSWER 13 OF 33 MEDLINE on STN
TI Specific T cell recognition of minimally homologous peptides: evidence for multiple endogenous ligands.

L16 ANSWER 14 OF 33 MEDLINE on STN
TI Modulation of T cell development by an endogenous altered peptide ligand.

L16 ANSWER 15 OF 33 MEDLINE on STN
TI Th2 cell clonal anergy as a consequence of partial activation.

L16 ANSWER 16 OF 33 MEDLINE on STN
TI Antagonism of superantigen-stimulated helper T-cell clones and hybridomas by altered peptide ligand.

L16 ANSWER 17 OF 33 MEDLINE on STN
TI Regulation of the costimulator B7, not class II major histocompatibility complex, restricts the ability of murine kidney tubule cells to stimulate CD4+ T cells.

L16 ANSWER 18 OF 33 MEDLINE on STN
TI Tickling the TCR: selective T-cell functions stimulated by altered peptide ligands.

L16 ANSWER 19 OF 33 MEDLINE on STN
TI Induction of T-cell anergy by altered T-cell-receptor ligand on live antigen-presenting cells.

L16 ANSWER 20 OF 33 MEDLINE on STN
TI Separation of T helper 1 clone cytolysis from proliferation and lymphokine production using analog peptides.

L16 ANSWER 21 OF 33 MEDLINE on STN
TI Dissection of the Hb(64-76) determinant reveals that the T cell receptor may have the capacity to differentially signal.

L16 ANSWER 22 OF 33 MEDLINE on STN
TI Complete dissection of the Hb(64-76) determinant using T helper 1, T helper 2 clones, and T cell hybridomas.

L16 ANSWER 23 OF 33 MEDLINE on STN
TI Stimulation of peripheral blood T cells by an activated T-cell line: a novel human autologous T-T lymphocyte reaction.

L16 ANSWER 24 OF 33 MEDLINE on STN
TI The processing and presentation of the self-antigen hemoglobin. Self-reactivity can be limited by antigen availability and costimulator expression.

L16 ANSWER 25 OF 33 MEDLINE on STN
TI T cell inducing determinants contain a hierarchy of residues contacting the T cell receptor.

L16 ANSWER 26 OF 33 MEDLINE on STN
TI Separation of IL-4 production from Th cell proliferation by an altered T cell receptor ligand.

L16 ANSWER 27 OF 33 MEDLINE on STN
TI T helper 2 (Th2) but not Th1 clones co-stimulate resting T cells in the presence of anti-CD3 monoclonal antibody.

L16 ANSWER 28 OF 33 MEDLINE on STN
TI Delayed antigen presentation by epidermal Langerhans cells to cloned T h1 and T h2 cells.

L16 ANSWER 29 OF 33 MEDLINE on STN
TI Direct activation of murine resting T cells by con A or anti-CD3 Ig.

L16 ANSWER 30 OF 33 MEDLINE on STN
TI Accessory cell function of Th2 clones.

L16 ANSWER 31 OF 33 MEDLINE on STN
TI Production of IL-2 and IFN by TH2 clones.

L16 ANSWER 32 OF 33 MEDLINE on STN
TI The syngeneic T-T lymphocyte reaction (STTLR). I. Induction of primary T anti-T cell proliferative responses in T cell cultures stimulated with self- and antigen-reactive T cells.

L16 ANSWER 33 OF 33 MEDLINE on STN
TI Antigenicity of passively acquired major histocompatibility antigens on T cells.

=> d l16,cbib,ab,1-33

L16 ANSWER 1 OF 33 MEDLINE on STN
2004065266. PubMed ID: 14768043. An MHC anchor-substituted analog of myelin oligodendrocyte glycoprotein 35-55 induces IFN-gamma and

autoantibodies in the absence of experimental autoimmune encephalomyelitis and optic neuritis. Ford Mandy L; **Evavold Brian D.** (Department of Microbiology and Immunology, Emory University, Atlanta 30322, USA.) European journal of immunology, (2004 Feb) 34 (2) 388-97. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Previous strategies to ameliorate experimental autoimmune encephalitis (EAE) include the treatment of autoreactive T cells with altered peptide ligands, which contain amino acid substitutions at TCR contact residues. We recently showed that a variant of myelin oligodendrocyte glycoprotein (MOG) 35-55 possessing low affinity for MHC (45D) induced anergy in MOG 35-55-specific T cells and reduced their encephalitogenicity upon adoptive transfer. Here we investigate the characteristics of the primary immune response to this MHC anchor-substituted peptide. Overall, we observed that immunization with 45D resulted in the production of IFN-gamma and anti-MOG 35-55 autoantibodies at levels similar to those of MOG 35-55-immunized mice with active EAE. However, no symptoms of clinical or histological EAE or overt histological optic neuritis were observed in 45D-immunized mice. Consistent with this finding, 45D-immunized mice did not exhibit CD4(+) infiltrates into the CNS. Therefore, MOG 35-55-specific precursors stimulated with a weak ligand (45D) mediate some EAE-associated effector functions but are unable to fully initiate the inflammatory process in the central nervous system that leads to clinical manifestation of EAE.

L16 ANSWER 2 OF 33 MEDLINE on STN

2003595670. PubMed ID: 14662853. CD43 modulates severity and onset of experimental autoimmune encephalomyelitis. Ford Mandy L; Onami Thandi M; Sperling Anne I; Ahmed Rafi; **Evavold Brian D.** (Department of Microbiology and Immunology, Emory University, Atlanta, GA 30322, USA.) Journal of immunology (Baltimore, Md. : 1950), (2003 Dec 15) 171 (12) 6527-33. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Experimental autoimmune encephalomyelitis (EAE) is a mouse model of multiple sclerosis characterized by infiltration of activated CD4(+) T lymphocytes into tissues of the CNS. This study investigated the role of CD43 in the induction and progression of EAE. Results demonstrate that CD43-deficient mice have reduced and delayed clinical and histological disease severity relative to CD43(+/+) mice. This reduction was characterized by decreased CD4(+) T cell infiltration of the CNS of CD43(-/-) mice but similar numbers of Ag-specific T cells in the periphery, suggesting a defect in T cell trafficking to the CNS. The absence of CD43 also affected cytokine production, as myelin oligodendrocyte glycoprotein (MOG) 35-55-specific CD43(-/-) CD4(+) T cells exhibited reduced IFN-gamma and increased IL-4 production. CD43(-/-) CD4(+) MOG-primed T cells exhibited reduced encephalitogenicity relative to CD43(+/+) cells upon adoptive transfer into naive recipients. These results suggest a role for CD43 in the differentiation and migration of MOG(35-55)-specific T cells in EAE, and identify it as a potential target for therapeutic intervention.

L16 ANSWER 3 OF 33 MEDLINE on STN

2003342219. PubMed ID: 12874212. Regulation of polyclonal T cell responses by an MHC anchor-substituted variant of myelin oligodendrocyte glycoprotein 35-55. Ford Mandy L; **Evavold Brian D.** (Department of Microbiology and Immunology, Emory University, Atlanta, GA 30322, USA.) Journal of immunology (Baltimore, Md. : 1950), (2003 Aug 1) 171 (3) 1247-54. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Analogs of immunogenic peptides containing substitutions at TCR contact residues (altered peptide ligands (APLs)) have been used to manipulate Ag-specific T cell responses in models of autoimmunity, including experimental autoimmune encephalomyelitis. However, recent clinical trials with APL of a myelin basic protein epitope revealed limitations of this therapy. In this study, we demonstrate that individual myelin oligodendrocyte glycoprotein (MOG) 35-55-specific T cell clones responded

differentially to a MOG 35-55 APL, raising questions about the ability of peptide analogs containing amino acid substitutions at TCR contact residues to control polyclonal populations of T cells. In contrast, we found that a variant peptide containing a substitution at an MHC anchor residue uniformly affected multiple MOG 35-55-specific clones and polyclonal lines. Stimulation of polyclonal MOG 35-55-specific T cells with an MHC variant peptide resulted in the induction of anergy, as defined by a dramatic reduction in proliferation and IL-2 production upon challenge with wild-type peptide. Furthermore, treatment of T cell lines with this peptide in vitro resulted in a significant reduction in their encephalitogenicity upon adoptive transfer. These results indicate that the use of MHC anchor-substituted peptides may be efficacious in the regulation of polyclonal T cell responses such as those found in EAE.

L16 ANSWER 4 OF 33 MEDLINE on STN

2003213443. PubMed ID: 12734331. Cutting edge: dependence of TCR antagonism on Src homology 2 domain-containing protein tyrosine phosphatase activity. Kilgore Neely E; Carter Jenny D; Lorenz Ulrike; **Evavold Brian D.** (Department of Microbiology and Immunology, Emory University, Atlanta, GA 30322, USA.) Journal of immunology (Baltimore, Md. : 1950), (2003 May 15) 170 (10) 4891-5. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The mechanism by which antagonist peptides inhibit T cell responses is unknown. Mice deficient in Src homology 2 domain-containing protein tyrosine phosphatase (SHP-1) have revealed its importance in the negative regulation of lymphocyte signaling. We investigated a possible role for SHP-1 in T cell antagonism and demonstrate, for the first time, a substantial increase in SHP-1 activity during antagonism of CD4(+) T cells. Furthermore, the removal of functional SHP-1 prevents antagonism in these cells. Our data demonstrate that T cell antagonism occurs via a negative intracellular signal that is mediated by SHP-1.

L16 ANSWER 5 OF 33 MEDLINE on STN

2003031363. PubMed ID: 12538680. TCR reserve: a novel principle of CD4 T cell activation by weak ligands. McNeil Lisa K; **Evavold Brian D.** (Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA.) Journal of immunology (Baltimore, Md. : 1950), (2003 Feb 1) 170 (3) 1224-30. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Some ligand-receptor systems have a receptor reserve where a maximal response can be achieved by occupation of a fraction of available receptors. An implication of a receptor reserve is the expansion of the number of ligands for response. To determine whether T cells follow receptor reserve, we have characterized the effect of reducing TCR levels on CD4 T cell responses elicited by altered peptide ligands that vary in potency. Agonist peptide is unaffected by a 90% reduction in TCR level while proliferation to weak agonists is significantly inhibited when TCR expression is reduced by 40%. Thymocyte-negative selection similarly demonstrates a differential requirement of TCR for response to agonist, weak agonist, and partial agonist. Therefore, our data demonstrate receptor reserve as a novel principle of T cell activation in which excess TCRs expand the antigenic repertoire to include less potent ligands.

L16 ANSWER 6 OF 33 MEDLINE on STN

2002197208. PubMed ID: 11904393. Dissociation of peripheral T cell responses from thymocyte negative selection by weak agonists supports a spare receptor model of T cell activation. McNeil Lisa K; **Evavold Brian D.** (Department of Microbiology and Immunology, Emory University, Atlanta, GA 30322, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2002 Apr 2) 99 (7) 4520-5. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We have focused on stability of the peptide-MHC complex as a determining factor of ligand potency for thymocytes and peripheral CD4+ T cell responses. MHC variant peptides that have low affinities and fast dissociation rates are different in that they stimulate proliferation and cytolysis of mature T cells (classifying the variant peptides as weak

agonists, but do not induce thymocyte negative selection. The MHC variant weak agonists require significant receptor reserve, because decreasing the level of T cell receptor on mature T cells blocks the proliferative response. These results demonstrate that peripheral T cells are more sensitive to MHC variant ligands by virtue of increased T cell receptor expression; in addition, the data support a T cell model of the spare receptor theory.

L16 ANSWER 7 OF 33 MEDLINE on STN

2001359974. PubMed ID: 11178343. Antimicrobial properties of porphyrins. Stojiljkovic I; **Evavold B D**; Kumar V. (Department of Microbiology and Immunology, Emory School of Medicine, 1510 Clifton Road, Atlanta, GA 30322, USA.. stojiljk@microbio.emory.edu) . Expert opinion on investigational drugs, (2001 Feb) 10 (2) 309-20. Ref: 90. Journal code: 9434197. ISSN: 1354-3784. Pub. country: England: United Kingdom. Language: English.

AB A large number of natural and synthetic porphyrins of diverse chemical compositions and characteristics can be isolated from nature or synthesised in the laboratory. Antimicrobial and antiviral activities of porphyrins are based on their ability to catalyse peroxidase and oxidase reactions, absorb photons and generate reactive oxygen species (ROS) and partition into lipids of bacterial membranes. Light-dependent, photodynamic activity of natural and synthetic porphyrins and pthalocyanines against Gram-positive and Gram-negative bacteria has been well demonstrated. Some non-iron metalloporphyrins (MPs) possess a powerful light-independent antimicrobial activity that is based on the ability of these compounds to increase the sensitivity of bacteria to ROS or directly produce ROS. MPs mimic haem in their molecular structure and are actively accumulated by bacteria via high affinity haem-uptake systems. The same uptake systems can be used to deliver antibiotic-porphyrin and antibacterial peptide-porphyrin conjugates. Haemin, the most well known natural porphyrin, possesses a significant antibacterial activity that is augmented by the presence of physiological concentrations of hydrogen peroxide or a reducing agent. Natural and synthetic porphyrins have relatively low toxicity in vitro and in vivo. The ability for numerous chemical modifications and the large number of different mechanisms by which porphyrins affect microbial and viral pathogens place porphyrins into a group of compounds with an outstanding potential for discovery of novel agents, procedures and materials active against pathogenic microorganisms.

L16 ANSWER 8 OF 33 MEDLINE on STN

2000243572. PubMed ID: 10779776. DO11.10 and OT-II T cells recognize a C-terminal ovalbumin 323-339 epitope. Robertson J M; Jensen P E; **Evavold B D**. (Department of Microbiology and Immunology, Emory University, Atlanta, GA 30322, USA.) Journal of immunology (Baltimore, Md. : 1950), (2000 May 1) 164 (9) 4706-12. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The OVA323-339 epitope recognized by DO11.10 (H-2d) and OT-II (H-2b) T cells was investigated using amino- and carboxy-terminal truncations to locate the approximate ends of the epitopes and single amino acid substitutions of OVA323-339 to identify critical TCR contact residues of the OVA323-339 peptide. DO11.10 and OT-II T cells are both specific for a C-terminal epitope whose core encompasses amino acids 329-337. Amino acid 333 was identified as the primary TCR contact residue for both cells, and amino acid 331 was found to be an important secondary TCR contact residue; however, the importance of other secondary TCR contact residues and peptide flanking residues differ between the cells. Additional OVA323-339-specific clones were generated that recognized epitopes found in the N-terminal end or in the center of the peptide. These findings indicate that OVA323-339 can be presented by I-Ad in at least three binding registers. This study highlights some of the complexities of peptide Ags such as OVA323-339, which contain a nested set of overlapping T cell epitopes and MHC binding registers.

L16 ANSWER 9 OF 33 MEDLINE on STN

1999369972. PubMed ID: 10490905. Cutting edge: dueling TCRs: peptide antagonism of CD4+ T cells with dual antigen specificities. Robertson J M; **Evavold B D**. (Department of Microbiology and Immunology, Emory University, Atlanta, GA 30322, USA.) Journal of immunology (Baltimore, Md. : 1950), (1999 Aug 15) 163 (4) 1750-4. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB T cells expressing two different TCRs were generated by interbreeding 3A9 and AND CD4+ TCR transgenic mice specific for the hen egg lysozyme (HEL) peptide 48-62:I-Ak and moth cytochrome c (MCC) peptide 88-103:I-Ek peptide:MHC ligands, respectively. Peripheral T cells in the offspring express two TCR V beta-chains and respond to HEL and MCC. We observed minimal or no additive effects upon simultaneous suboptimal stimulation with both agonist peptides; however, an antagonist peptide for the 3A9 TCR was able to inhibit the response of the dual receptor T cells to MCC, the AND TCR agonist. This HEL antagonist peptide did not affect AND single transgenic T cells, indicating that the antagonism observed in the dual TCR cells is dependent on the presence of the HEL-specific 3A9 TCR. In contrast, anti-TCR Abs mediate receptor-specific antagonism. These results demonstrate that peptide antagonism exerts a dominant effect.

L16 ANSWER 10 OF 33 MEDLINE on STN

1998317019. PubMed ID: 9653085. Conserved T cell receptor repertoire in primary and memory CD8 T cell responses to an acute viral infection. Sourdive D J; Murali-Krishna K; Altman J D; Zajac A J; Whitmire J K; Pannetier C; Kourilsky P; **Evavold B**; Sette A; Ahmed R. (Emory Vaccine Center, Rollins Research Center, Emory University, Atlanta, Georgia 30322, USA.) Journal of experimental medicine, (1998 Jul 6) 188 (1) 71-82. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Viral infections often induce potent CD8 T cell responses that play a key role in antiviral immunity. After viral clearance, the vast majority of the expanded CD8 T cells undergo apoptosis, leaving behind a stable number of memory cells. The relationship between the CD8 T cells that clear the acute viral infection and the long-lived CD8 memory pool remaining in the individual is not fully understood. To address this issue, we examined the T cell receptor (TCR) repertoire of virus-specific CD8 T cells in the mouse model of infection with lymphocytic choriomeningitis virus (LCMV) using three approaches: (a) in vivo quantitative TCR beta chain V segment and complementarity determining region 3 (CDR3) length repertoire analysis by spectratyping (immunoscope); (b) identification of LCMV-specific CD8 T cells with MHC class I tetramers containing viral peptide and costaining with TCR Vbeta-specific antibodies; and (c) functional TCR fingerprinting based on recognition of variant peptides. We compared the repertoire of CD8 T cells responding to acute primary and secondary LCMV infections, together with that of virus-specific memory T cells in immune mice. Our analysis showed that CD8 T cells from several Vbeta families participated in the anti-LCMV response directed to the dominant cytotoxic T lymphocyte (CTL) epitope (NP118-126). However, the bulk (approximately 70%) of this CTL response was due to three privileged T cell populations systematically expanding during LCMV infection. Approximately 30% of the response consisted of Vbeta10+ CD8 T cells with a beta chain CDR3 length of nine amino acids, and 40% consisted of Vbeta8.1+ (beta CDR3 = eight amino acids) and Vbeta8.2+ cells (beta CDR3 = six amino acids). Finally, we showed that the TCR repertoire of the primary antiviral CD8 T cell response was similar both structurally and functionally to that of the memory pool and the secondary CD8 T cell effectors. These results suggest a stochastic selection of memory cells from the pool of CD8 T cells activated during primary infection.

L16 ANSWER 11 OF 33 MEDLINE on STN

1998080599. PubMed ID: 9419214. Persistence of peptide-induced CD4+ T cell anergy in vitro. Ryan K R; **Evavold B D**. (Department of Microbiology and Immunology, Emory University, Atlanta, Georgia 30322, USA.) Journal of experimental medicine, (1998 Jan 5) 187 (1) 89-96. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Clonal T cell unresponsiveness, or anergy, has been proposed as a

mechanism of peripheral tolerance in vivo, and as a potential means of curbing unwanted T cell responses. In this study, anergy was induced in a T helper cell (Th) clone reactive to hemoglobin (Hb) peptide 64-76 by coculture of the T cells with live antigen-presenting cells (APCs) and 74L, a peptide analog of Hb(64-76) that contains a single amino acid substitution of leucine for glycine at position 74, or with a low concentration of the agonist ligand. The anergic state was characterized by blunted proliferation and interleukin (IL) 2 production upon restimulation with Hb(64-76), and was not the result of impaired TCR/CD3 downmodulation. The addition of exogenous IL-12 transiently restored proliferation of the anergic lines, but removal of IL-12 from culture returned the T cells to their nonproliferative state. Interestingly, persistence of the anergic phenotype was observed despite biweekly restimulation with antigen, APCs, and IL-2. Thus, T cell unresponsiveness induced by a peptide produced a stable, persistent anergic state in a Th0 clone that was not reversible by stimulation with IL-2 or -12.

L16 ANSWER 12 OF 33 MEDLINE on STN

97002457. PubMed ID: 8849454. Enhanced dissociation of HLA-DR-bound peptides in the presence of HLA-DM. Weber D A; **Evavold B D**; Jensen P E. (Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA.) Science, (1996 Oct 25) 274 (5287) 618-20. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Human leukocyte antigen (HLA)-DM is a critical participant in antigen presentation that catalyzes the release of class II-associated invariant chain-derived peptides (CLIP) from newly synthesized class II histocompatibility molecules, freeing the peptide-binding site for acquisition of antigenic peptides. The mechanism for the selective release of CLIP but not other peptides is unknown. DM was found to enhance the rate of peptide dissociation to an extent directly proportional to the intrinsic rate of peptide dissociation from HLA-DR, regardless of peptide sequence. Thus, CLIP is rapidly released in the presence of DM, because its intrinsic rate of dissociation is relatively high. In antigen presentation, DM has the potential to markedly enhance the rate of peptide exchange, favoring the presentation of peptides with slower intrinsic rates of dissociation.

L16 ANSWER 13 OF 33 MEDLINE on STN

95316721. PubMed ID: 7540944. Specific T cell recognition of minimally homologous peptides: evidence for multiple endogenous ligands. **Evavold B D**; Sloan-Lancaster J; Wilson K J; Rothbard J B; Allen P M. (Department of Pathology Washington University School of Medicine, St. Louis, Missouri 63110, USA.) Immunity, (1995 Jun) 2 (6) 655-63. Journal code: 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB The T cell receptor (TCR) can interact with a spectrum of peptides as part of its ligand, including the immunogenic peptide, variants of this peptide,and apparently unrelated peptides. The basis of this broad specificity for ligand was investigated by substitution analysis of a peptide antigen and functional testing using a B cell apoptosis assay. A peptide containing as few as 1 aa in common with this peptide could stimulate a specific T cell response. Two endogenous ligands, an agonist and a partial agonist, were readily identified from a search of the SwissProt database, indicating that multiple endogenous ligands likely exist for a given T cell. These findings strongly support the concept that one TCR has the ability to interact productively with multiple different ligands, and provide evidence that such ligands exist in the endogenous peptide repertoire.

L16 ANSWER 14 OF 33 MEDLINE on STN

95138715. PubMed ID: 7836933. Modulation of T cell development by an endogenous altered peptide ligand. Hsu B L; **Evavold B D**; Allen P M. (Center for Immunology, Washington University School of Medicine, St. Louis, Missouri 63110.) Journal of experimental medicine, (1995 Feb 1) 181 (2) 805-10. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB T cells potentially encounter numerous endogenous peptides during selection in the thymus and in the periphery. We examined the impact of an endogenous peptide on in vivo T cell development, using a TCR transgenic mouse model based on a hemoglobin-specific T cell clone. In these mice, the transgenic beta chains paired with endogenous alpha chains. This led to a serendipitous primary reactivity to Ser69 peptide, an altered peptide ligand of the Hbd (64-76) epitope of the parent clone. Two Ser69-reactive T cell populations were identified. A smaller population of the Ser69-reactive T cells responded both to Ser69 and Hbd (64-76). A majority reacted only to Ser69, and not to Hbd(64-76); in fact, Hbd(64-76) was a specific TCR antagonist for these Ser69-only-reactive T cells. Thus, in this unique experimental system, Ser69 became an agonist, and Hbd (64-76) was an antagonist. Endogenous presentation of the antagonist ligand in the thymus selectively eliminated the high-avidity cells, while sparing low-avidity cells in the Ser69-reactive T cell repertoire. These results highlight how specificity guides developing T cells through a network of ligands and indicate that the endogenous peptide pool has a profound effect on T cell development and repertoire.

L16 ANSWER 15 OF 33 MEDLINE on STN

95016411. PubMed ID: 7931057. Th2 cell clonal anergy as a consequence of partial activation. Sloan-Lancaster J; **Evavold B D**; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, Missouri 63110.) Journal of experimental medicine, (1994 Oct 1) 180 (4) 1195-205. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB We have demonstrated Th2 clonal anergy as a consequence of partial T cell activation by immunogenic peptide and chemically fixed APC, as well as by altered peptide ligand and live antigen-presenting cells (APC). Either stimulation resulted in a profound inability of the T cells to proliferate upon restimulation with antigen and functional APC, a similar phenomenon to that found with Th1 cells. The anergic state was long lasting and was restricted to proliferation, since the T cells retained the ability to produce cytokines upon restimulation, albeit at slightly reduced levels. Th2 anergy induction was inhibited by cyclosporine A, but not by provision of exogenous costimulation or growth factors. The data presented unify Th1 and Th2 cells with regard to anergy and suggest that the fundamental control during anergy for both subsets is prevention of clonal expansion, thus blocking amplification of the immune response.

L16 ANSWER 16 OF 33 MEDLINE on STN

94181580. PubMed ID: 8134391. Antagonism of superantigen-stimulated helper T-cell clones and hybridomas by altered peptide ligand. **Evavold B D**; Sloan-Lancaster J; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Proceedings of the National Academy of Sciences of the United States of America, (1994 Mar 15) 91 (6) 2300-4. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB T-cell activation by an immunogenic peptide can be antagonized by nonstimulatory analogs of that peptide. We investigated this T-cell receptor antagonism by using staphylococcal enterotoxin superantigen to stimulate hemoglobin-specific helper T (Th) cells because its activation pathway may differ from that of conventional antigen. Interestingly, superantigen activation of these Th cells was antagonized by hemoglobin peptide analogs even though agonist (superantigen) and antagonist (analog peptide) bind at different sites on the major histocompatibility complex-encoded molecule and the T-cell receptor. The antagonism appeared to be a fundamental block in T-cell activation, as phosphoinositol generation, cytokine production, and proliferation were reduced in Th1 clones, and, similarly, proliferative and cytokine responses were inhibited in Th2 cells. Even T-cell hybridoma activation (cytokine production and apoptosis) was inhibited by peptide antagonists. Furthermore, analog peptides that functioned as partial agonists for these Th cells also antagonized superantigen-induced proliferation and thus were a subset of the peptide antagonists. In summary, our results demonstrate

that analogs of immunogenic peptide are potent antagonists for in cell responses induced by superantigen as well as immunogenic peptide.

L16 ANSWER 17 OF 33 MEDLINE on STN

94179468. PubMed ID: 7510717. Regulation of the costimulator B7, not class II major histocompatibility complex, restricts the ability of murine kidney tubule cells to stimulate CD4+ T cells. Hagerty D T; **Evavold B D;** Allen P M. (Department of Medicine, Jewish Hospital, St. Louis, Missouri.) Journal of clinical investigation, (1994 Mar) 93 (3) 1208-15. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB The proximal segment of murine kidney tubule cells (KTC) constitutively expresses low levels of class II major histocompatibility complex (MHC) that are upregulated during local and systemic inflammation. It is not known if KTC also express the costimulator molecules necessary for them to productively participate in immune responses and stimulate T cells. To answer this question, we studied the ability of KTC to present antigens to four Th1 clones. KTC did not induce T cell proliferation to specific antigen, superantigen, or concanavalin A. However, T cell receptors did engage the peptide/MHC ligand presented by KTC, as indicated by T cell enlargement and upregulation of interleukin-2 receptor expression. Importantly, KTC failed to express the Th1 costimulator, B7, as detected by fluorescence cytometry and reverse transcription polymerase chain reaction. We directly demonstrated that lack of B7 expression accounted for at least part of the KTC presentation defect, in that a KTC line transfected with the cDNA for B7 stimulated T cell proliferation to antigen. Our results suggest that epithelial cells expressing class II MHC have developed mechanisms to prevent costimulator expression and limit parenchymal tissue destruction. Failure of class II-expressing epithelial cells to limit costimulator expression may be an important component of organ-specific autoimmunity.

L16 ANSWER 18 OF 33 MEDLINE on STN

94137363. PubMed ID: 8305133. Tickling the TCR: selective T-cell functions stimulated by altered peptide ligands. **Evavold B D;** Sloan-Lancaster J; Allen P M. (Dept of Pathology, Washington University School of Medicine, St Louis, MO 63110.) Immunology today, (1993 Dec) 14 (12) 602-9. Ref: 60. Journal code: 8008346. ISSN: 0167-5699. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Recent observations of T-cell responses following T-cell receptor (TCR) interaction with altered peptide ligands have highlighted the complexity of this signalling system. The indications are that the TCR responds to minor changes in ligand with gradations of T-cell activation and effector functions. Brian Evavold, Joanne Sloan-Lancaster and Paul Allen review these studies and present a model in which partial T-cell activation and TCR antagonism are related events in a continuum of signalling through the TCR.

L16 ANSWER 19 OF 33 MEDLINE on STN

93247637. PubMed ID: 8483498. Induction of T-cell anergy by altered T-cell-receptor ligand on live antigen-presenting cells. Sloan-Lancaster J; **Evavold B D;** Allen P M. (Department of Pathology, Washington University School of Medicine, St Louis, Missouri 63110.) Nature, (1993 May 13) 363 (6425) 156-9. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Activation of CD4+ T helper cells results from the occupancy of the T-cell receptor (TCR) by immunogenic peptide bound to a class II major histocompatibility complex (MHC) molecule, together with a co-stimulatory signal from the antigen-presenting cell (APC). This activation leads to proliferation, cytokine production (Th1 or Th2 profile) and cytolysis. Engagement of the TCR in the absence of co-stimulation causes Th1 cells to become unresponsive to subsequent antigenic stimulation. We have previously demonstrated that analogues of an immunogenic peptide could stimulate Th1 and Th2 cells to carry out some effector functions without inducing proliferation, a phenomenon we term partial activation. Here we study the consequences of such partial activation through the TCR of two

Th1 clones using peptide analogues presented by a live APC. A peptide analogue that is unable to stimulate clonal proliferation or production of cytokine or inositol phosphate can induce the T cells to become profoundly unresponsive to subsequent stimulation with the immunogenic peptide. Thus, altering the ligand of the TCR by using a peptide analogue on a functional APC sends a signal to Th1 clones that results in anergy.

L16 ANSWER 20 OF 33 MEDLINE on STN

93224717. PubMed ID: 8468461. Separation of T helper 1 clone cytolysis from proliferation and lymphokine production using analog peptides. **Evavold B D**; Sloan-Lancaster J; Hsu B L; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Journal of immunology (Baltimore, Md. : 1950), (1993 Apr 15) 150 (8 Pt 1) 3131-40. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB In this report, we investigate the activation of Th1 clones using altered TCR ligand. By changing the immunogenic peptide, cytolytic function can be separated from proliferative and lymphokine responses. These three responses were examined and dissected in two Th1 clones using analogs of the murine hemoglobin [Hb(64-76)] peptide. This analysis was focused on amino acids in the immunogenic peptide that were possible T cell contact residues. Typically, several amino acids were identified as critical contact residues for a Th1 proliferative response. An examination of lymphokine production (IFN-gamma or IL-3) revealed the same pattern of response to the analog peptides indicating that the proliferative and lymphokine responses were directly related. However, for cytolysis, fewer amino acid residues were identified as critical contact residues for effector function. Thus, some altered peptide ligands allowed the disassociation of the cytolytic function from the proliferative and lymphokine responses in Th1 clones. To extend these findings, the activation of T cell hybridomas created from the Th1 clones were similarly examined using the altered TCR ligands. The lymphokine response (IL-2) of the T cell hybridomas identified the same critical amino acids as did the cytolytic response of the Th1 clones. Thus, analog peptides partially activated the Th1 clones such that cytolysis occurred independent from proliferative and lymphokine responses.

L16 ANSWER 21 OF 33 MEDLINE on STN

93135036. PubMed ID: 1485563. Dissection of the Hb(64-76) determinant reveals that the T cell receptor may have the capacity to differentially signal. **Evavold B D**; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Advances in experimental medicine and biology, (1992) 323 17-21. Ref: 10. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

L16 ANSWER 22 OF 33 MEDLINE on STN

92105725. PubMed ID: 1370311. Complete dissection of the Hb(64-76) determinant using T helper 1, T helper 2 clones, and T cell hybridomas. **Evavold B D**; Williams S G; Hsu B L; Buus S; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Journal of immunology (Baltimore, Md. : 1950), (1992 Jan 15) 148 (2) 347-53. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We have generated cloned Th1 cells, Th2 cells, and T cell hybridomas specific for the single immunogenic peptide from the beta-chain of murine hemoglobin (Hb(64-76)). The availability of these various types of T cells provided us an unique opportunity to examine and dissect the T cell response to an immunogenic peptide. A panel of altered Hb peptides was made by replacing each amino acid in the Hb peptide (positions 64-76) with a conservative amino acid substitution or an alanine. Although none of the eleven T cell clones and hybridomas tested exhibited the same pattern of reactivity to the substituted Hb peptides, some general features were identified for all T cell responses. The primary T cell contact residue of Hb(64-76) was shown to be asparagine 72. For every Hb(64-76) specific T cell, no activation was observed using a peptide containing the

conservative substitution of a glutamine for the asparagine at position 72. The flanking glutamic acid at position 73 was also required for a proliferative response for all of the Th1 and Th2 clones. The Th subtypes were not grossly unique in their responses to the substituted Hb peptides, but exhibited minor differences in fine specificity with the Th1 cells identifying more critical amino acids then did the Th2 cells. For the Th1 cells and also the T cell hybridomas, the phenylalanine at position 71 was critical for a T cell response. Analysis of peptide affinity for IEk molecules indicated that position 71 played a role in peptide binding to MHC. Secondary T cell contact residues, which were important for many but not all of the T cells, were identified at positions 69, 70, and 76. Overall T cell responses were minimally affected by changes in the amino acid residues at positions 64-68, 74, and 75. We have also demonstrated that cloned Th1 cells, Th2 cells and T hybridomas can be generated against the same Hb(64-76) determinant.

L16 ANSWER 23 OF 33 MEDLINE on STN

92086825. PubMed ID: 1684247. Stimulation of peripheral blood T cells by an activated T-cell line: a novel human autologous T-T lymphocyte reaction. Ditzian-Kadanoff R; Parks L; **Evavold B**; Quintans J; Swartz T J. (Department of Medicine, University of Chicago, Illinois.) Scandinavian journal of immunology, (1991 Dec) 34 (6) 713-9. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB T lymphocyte interactions have generally been described between discrete functional subsets. In our investigation of murine T-cell interactions we described a type of T-T interaction termed the 'Syngeneic T-T Lymphocyte Reaction' in which activated T-cell clones stimulated the proliferation of resting T cells mainly through a mechanism involving cell to cell contact. To investigate whether similar reactions occur in the human immune system we used the human autoreactive T-cell line C.1 to stimulate peripheral T cells. Line C.1 cells, which are not transformed and do not secrete IL2, consistently caused proliferation of purified freshly isolated autologous peripheral human T cells as measured by a [3H]-thymidine incorporation assay. The proliferation was seen in both the CD4 and CD8 subsets and could be inhibited with anti-DR and anti-CD2 antibodies. The stimulation is not due to carryover of classical antigen-presenting cells or to the C.1 line cells acting as antigen-presenting cells. We propose that some activated T cells, probably by expression of a surface molecule, can stimulate resting T cells thereby allowing for antigen-non-specific augmentation of the immune response.

L16 ANSWER 24 OF 33 MEDLINE on STN

92043688. PubMed ID: 1834734. The processing and presentation of the self-antigen hemoglobin. Self-reactivity can be limited by antigen availability and costimulator expression. Hagerty D T; **Evavold B D**; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Journal of immunology (Baltimore, Md. : 1950), (1991 Nov 15) 147 (10) 3282-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB APC do not distinguish between self- and foreign proteins. Previous studies from our laboratory demonstrated that most endogenous host APC constitutively processed and presented the self-Ag, hemoglobin (Hb), as detected by the Hb-specific T cell hybridoma, YO1.6. We have now examined APC in organs known to be involved in RBC degradation (liver Kupffer cells and splenic small resting B cells) for the presence of Hb/Ia complexes and for the expression of the costimulation necessary to trigger proliferation of T cell clones. We detected Hb/Ia complexes not only on splenic small resting B cells, but also on liver Kupffer cells. Interestingly, complexes were not present on lymph node small resting B cells. Splenic small resting B cells expressed costimulatory activity and efficiently stimulated the Th2 clones only. The opposite pattern was observed with liver Kupffer cells, which expressed costimulatory activity for Th1 clones only. However, if costimulatory activity was provided for the Th2 clones (IL-1 beta) and Th1 clones (allogenic spleen cells), the clones did proliferate in response to Kupffer cells and small resting B cells,

respectively. In this report we have demonstrated that 1) endogenously formed self Hb/Ia complexes are expressed on splenic small resting B cells and liver Kupffer cells but not on lymph node small resting B cells and 2) these APC are also able to limit the expression of costimulatory activity for Th2 and Th1 T cell clones. Thus, endogenous APC not only constitutively process and present the self-Ag Hb, but also limit expression of the costimulatory activity necessary to trigger T cell proliferation against a self-Ag. The constitutive processing and presentation of self-Ag, as well as the regulation of costimulatory activity on APC, is likely an important feature of the maintenance of self-tolerance.

L16 ANSWER 25 OF 33 MEDLINE on STN

92032816. PubMed ID: 1718483. T cell inducing determinants contain a hierarchy of residues contacting the T cell receptor. **Evavold B D;** Williams S G; Chen J S; Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Seminars in immunology, (1991 Jul) 3 (4) 225-9. Ref: 31. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB T cells through their antigen specific T cell receptor recognize a bi-molecular ligand composed of an antigenic peptide bound to a MHC molecule. Several T cell inducing determinants have been extensively characterized by single amino acid substitutions. In this review, we have summarized our characterization of four immunodominant determinants. Each of these determinants possessed a single amino acid residue which was absolutely critical for the recognition by T cells. From these data we propose a hypothesis that there is a hierarchy in the T cell contact residues of a determinant, composed of a single primary residue, and a few secondary residues.

L16 ANSWER 26 OF 33 MEDLINE on STN

92022522. PubMed ID: 1833816. Separation of IL-4 production from Th cell proliferation by an altered T cell receptor ligand. **Evavold B D;** Allen P M. (Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110.) Science, (1991 May 31) 252 (5010) 1308-10. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB In the presence of antigen presenting cells, a murine T helper (Th) cell specific for murine hemoglobin (Hb) responded to its immunogenic peptide by both cytokine (interleukin-4) secretion and proliferation. An altered Hb peptide with a single amino acid substitution induced only cytokine secretion and did not induce proliferation. Interleukin-1 costimulated and restored the Th proliferative response to normal levels. The altered peptide also supported cognate T cell-B cell interactions indicative of T cell helper function. Thus, this result suggests that the T cell receptor has the capacity of differential signaling.

L16 ANSWER 27 OF 33 MEDLINE on STN

91207944. PubMed ID: 2535137. T helper 2 (Th2) but not Th1 clones co-stimulate resting T cells in the presence of anti-CD3 monoclonal antibody. **Evavold B D;** Yokoyama A; Hirsch R; Bluestone J A; Quintans J. (Committee on Immunology, University of Chicago, IL 60637.) International immunology, (1989) 1 (4) 443-9. Journal code: 8916182. ISSN: 0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We have investigated the effects of monoclonal antibody (mAb) to the CD3 epsilon protein on interactions between small, resting T cells and antigen-specific T helper clones. Highly purified, splenic T cells lacking identifiable accessory cells do not proliferate in a thymidine uptake assay to anti-CD3 mAb, Con A, rIL-2, rIL-4, or irradiated T helper clones (both Th1 and Th2). However, the responding T cells proliferate significantly to the combined stimulus of Th2 clones and anti-CD3 antibody. Only the Th2, not the Th1, subpopulation of T helper cells has the ability to induce a T cell response. The Th2 cell-dependent activation of small resting T cells does not require the external cross-linkage of the anti-CD3 mAb via Fc receptor expressing cells or the secretion of lymphokines from the Th2 helper clones, but it is inhibitable

by anti-LFA-1 antibody. Thus, Th2 clones provide a co-stimulatory signal which in conjunction with anti-CD3 mAb causes resting T cell proliferation in the absence of conventional accessory cells.

L16 ANSWER 28 OF 33 MEDLINE on STN

91010900. PubMed ID: 2212728. Delayed antigen presentation by epidermal Langerhans cells to cloned T h1 and T h2 cells. Tiegs S L; **Evavold B D;** Yokoyama A; Stec S; Quintans J; Rowley D. (Department of Pathology, University of Chicago, Illinois.) Journal of investigative dermatology, (1990 Oct) 95 (4) 446-9. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Langerhans (LC) cells require incubation with protein antigen for several days before the cells effectively stimulate proliferation of cloned, H-2 restricted, antigen-specific T h cells. In contrast, splenic antigen-presenting cells are immediately effective. LC are immediately competent, however, if an immunogenic peptide rather than the intact protein is the immunogen, indicating that resident or unchallenged LC have the required class II MHC and can provide the signals necessary for T-cell proliferation but may lack the capacity to internalize or cleave protein antigens. We propose that delayed antigen presentation by LC may be intrinsic and advantageous for promoting early systemic immunity. LC stimulate cloned T h1 and T h2 cells equally well, suggesting that LC may not limit or bias the type of immunity that occurs with cutaneous antigenic challenge.

L16 ANSWER 29 OF 33 MEDLINE on STN

90121569. PubMed ID: 2532886. Direct activation of murine resting T cells by con A or anti-CD3 Ig. Quintans J; Yokoyama A; **Evavold B;** Hirsch R; Mayforth R D. (Department of Pathology, University of Chicago, IL 60637.) Journal of molecular and cellular immunology : JMCI, (1989) 4 (4) 225-35; discussion 235-7. Journal code: 8405005. ISSN: 0724-6803. Pub. country: United States. Language: English.

AB The induction of antigen-specific T cell activation is highly dependent on accessory cells (AC) which present processed antigenic fragments associated with MHC molecules and provide costimulatory signals for T cells. Antigen-specific T cell activation requires cross-linking of the TCR and the reception of one or more nonantigen-specific signals which eventually lead to T cell activation and proliferation. This sequence of events can be mimicked by lectins, bacterial enterotoxins, and anti-TCR antibodies in conjunction with APC or the combination of phorbol esters and Ca ionophores. Although the combination of PMA + Ca ionophore and certain types of T-T interactions result in APC independent T cell activation, it is generally assumed that physiologic T cell activation requires APC. The seemingly direct activation of T cells by other T cells is rather surprising in view of the known APC dependence of antigen, lectin and anti-TCR mediated T cell activation. It is conceivable that T cell mediated T cell activation is due to "cryptic" APC contamination because the total absence of APC is difficult to disprove. In reality, neither total depletion nor residual contamination with APC can be proven or disproven experimentally. Thus it can be legitimately argued that both APC dependent and independent T cell activation occur, albeit under different experimental conditions. For instance, it is possible that APC independent activation of T cells by lectins and anti-TCR antibodies would require high concentrations of activators to overide their dependence on APC. It is also conceivable and, in our opinion quite likely, that once activated, T cells could propagate T cell activation through T-T interactions. In this report we test two hypotheses: (1) The triggering of resting T cells leading to autocrine cell proliferation depends entirely on cross-linking TCR molecules, and (2) The presence of activated T cells facilitates TCR mediated activation of resting T cells without the participation of conventional APC. We present evidence that highly purified, small resting T cells can be reproducibly activated with high doses of ConA, plastic bound anti-CD3 mab and its F(ab')2 fragments. This APC independent response results in blastic transformation, expression of the IL2 Receptor, the secretion of IL2 and significant proliferation of both CD4+ and CD8+ murine T cells. These observations demonstrate that

vigorous cross linking of TCRs by anti CD3 mab and, presumably ConA, is sufficient to induce T cell activation and autocrine (IL2 driven) proliferation.(ABSTRACT TRUNCATED AT 400 WORDS)

L16 ANSWER 30 OF 33 MEDLINE on STN

89381308. PubMed ID: 2528580. Accessory cell function of Th2 clones. **Evavold B D**; Quintans J. (Department of Pathology, University of Chicago, IL 60637.) Journal of immunology (Baltimore, Md. : 1950), (1989 Sep 15) 143 (6) 1784-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We have investigated the ability of T helper clones to serve as accessory cells and in the presence of mitogen activate freshly-isolated, splenic T cells. In this type of costimulatory assay, the Th cells that secrete IL-4 but not the Th cells that secrete IL-2 function as AC to induce T cell proliferation in the presence of various T cell mitogens (Con A, anti-CD3 mAb, anti-TCR mAb, and anti-Thy-1 mAb). The signal provided by the accessory Th2 cells occurred independently of MHC restriction, and the analysis of dose-response curves showed the involvement of a single stimulator cell. CD4, as well as CD8 expressing splenic T cells were induced to proliferate by the Th2 clones and mitogen, but mAb specific for CD4 or CD8 failed to affect the response. These findings indicate that cloned Th2 cells functioned as accessory cells and induced naive T cells to proliferate in the presence of mitogen.

L16 ANSWER 31 OF 33 MEDLINE on STN

89358125. PubMed ID: 2570041. Production of IL-2 and IFN by TH2 clones. Yokoyama A; **Evavold B**; Dunn D E; Quintans J. (Department of Pathology, University of Chicago, IL 60637.) Immunology letters, (1989 May) 21 (2) 119-25. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB We have studied the production of IL-2, IL-4 and IFN-gamma by a panel of CD4+ clones produced in our laboratory. The clones were classified as TH1 and TH2 because of their ability to secrete IL-2 or IL-4, respectively, following stimulation with APC + Ag and by their characteristic proliferative responses to exogenous IL-2 or IL-4. Some of the TH2 clones, all of which happened to be autoreactive, produced IL-2 and one of these, as well as one antigen-reactive TH2 clone, also secreted IFN-gamma following stimulation with immobilized anti-CD3 mAb. IL-2 production by TH2 cells required higher concentrations of anti-CD3 mAb than IL-4 production. Thus, the TH2 clones seem to be heterogeneous. We designate the IL-2/IL-4 secretors as TH2B and those making IL-4 as TH2A clones.

L16 ANSWER 32 OF 33 MEDLINE on STN

89322712. PubMed ID: 3509918. The syngeneic T-T lymphocyte reaction (STTLR). I. Induction of primary T anti-T cell proliferative responses in T cell cultures stimulated with self- and antigen-reactive T cells. Suzuki H; **Evavold B**; Swartz T J; Latta S L; Quintans J. (Department of Pathology, University of Chicago, IL 60649.) Journal of molecular and cellular immunology : JMCI, (1986) 2 (6) 331-44. Journal code: 8405005. ISSN: 0724-6803. Pub. country: United States. Language: English.

AB The generally accepted "Gershonian" view of immunoregulation attributes T cell-mediated regulation of immune responses to the activities of discrete T cell subsets with specialized functions such as help, suppression, and contrasuppression. Several observations made in our laboratory are not compatible with this paradigm. For instance, careful quantitations of carrier-specific T cell help to hapten-specific B cells in an adoptive transfer system yielded complex dose-response curves that could not be explained on the basis of interactions between discrete subsets of helper and suppressor cells. Rather, the results were most easily interpreted according to a model based on the following assumptions: (1) Regulation of helper T cell activity is a dose-dependent, dynamic property of T cell populations that exhibit a high degree of connectivity (self-recognition) and (2) helper T cells have the ability to perform different functions, depending on the current activity of other interacting lymphocytes. A good example of cloned T cells capable of performing multiple immunoregulatory functions was provided by the IEk-specific self-reactive

Lbd line which provided help, suppression, and contrasuppression to T cell dependent PFC responses (see Quintans et al., 1986). Since these effects were strictly dependent on the levels of antigen-specific T cell help, we hypothesized that Lbd cells interacted with other T cells to modulate their function. In this paper, we directly test the hypothesis that activated T cells can interact directly with resting T cells and describe the proliferative component of a syngeneic T cell anti-T cell response induced by antigen and self-reactive helper and cytotoxic T cells. In a follow-up report, we will describe the effector component of the T anti-T cell response.(ABSTRACT TRUNCATED AT 400 WORDS)

L16 ANSWER 33 OF 33 MEDLINE on STN

88278429. PubMed ID: 3260698. Antigenicity of passively acquired major histocompatibility antigens on T cells. Swartz T J; **Evavold B**; Suzuki H; Yokoyama A; Quintans J. (Department of Medicine, University of Chicago, Illinois 60637.) Transplantation, (1988 Jul) 46 (1) 137-43. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

AB T cell blasts and lines passively acquire MHC molecules in vitro. To determine the role of these molecules in immunoregulatory reactions, we examined whether T cell lines grown on irradiated F1 spleen cells were able to supply allogeneic MHC antigens for the stimulation of T cell proliferation. Immunofluorescence analysis demonstrates that autoreactive T cell lines grown with irradiated F1 spleen cells acquire allogeneic class II molecules and subsequently lose the MHC molecules within 4 days of coculture with syngeneic cells. The proliferative response of (H-2k x H-2d)F1T cells stimulated by a T cell line grown on (H-2k x H-2d)F1 cells is inhibited by the addition of hybridoma-culture supernatants containing anti-IAd as well as anti-IEk antibodies. The proliferation of the F1 T cells to the T cell line grown on H-2k spleen cells is only affected by supernatants containing anti-IEk antibodies. To investigate the role of acquired class I MHC antigens, we examined their ability to serve as antigens for cytotoxic cells. Anti-H-2k cytotoxic T cells are generated when H-2b T cells are cultured with an H-2b-derived T cell line, only if the line has been grown on (H-2k x H-2b)F1 cells. An H-2b-derived T cell line exposed to (H-2k x H-2b)F1 cells can be lysed by anti-H-2k cytotoxic T cells from a primary MLR. Similarly, an H-2k anti-H-2b cytotoxic T cell clone will kill an H-2k-derived T cell clone grown on (H-2k x H-2b)F1 spleen cells. These results demonstrate that passively acquired class I molecules can stimulate the generation of cytotoxic T cells that lyse cells expressing the class I antigens and that passively acquired class I molecules expressed on T cells serve as the target for cytotoxic T cells.

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(FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
E MARCHALONIS JOHN J/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
E MARCHALONIS J J/IN
L2 5 S E2 OR E3

FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
E MARCHALONIS J J/AU
L3 256 S E2-E5
L4 75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5 4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6 0 S L4 AND (TH1 (W) TH2)

FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7 9668 S (TCR OR T-CELL RECEPTOR)
L8 7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)

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L9            618 S L8 AND (V BETA)
L10           123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11            39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12            38 S L11 NOT L1

     FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004
L13         24107 S (T CELL RECEPTOR OR TCR)
L14          1326 S L13 AND (TH1 OR TH2 OR T-HELPER 1 OR T-HELPER 2)
L15            18 S L14 AND (ALTERED PEPTIDE LIGANDS)
                  E EVAVOLD B D/AU
L16            33 S E2-E4

=> e madrenas j/au
E1             2     MADREN WHALLEY J S/AU
E2             1     MADREN WHALLEY JANNA S/AU
E3            54 --> MADRENAS J/AU
E4            11     MADRENAS JOAQUIN/AU
E5             3     MADRENAS PUIG J/AU
E6             7     MADRENYS BRUNET N/AU
E7             9     MADRENYS N/AU
E8             1     MADREPERLA S/AU
E9            23     MADREPERLA S A/AU
E10            1     MADREPERLA STEVEN A/AU
E11            1     MADRERA ROBERTO RODRIGUEZ/AU
E12            3     MADRERO Y/AU

=> s e3 or e4
              54 "MADRENAS J"/AU
              11 "MADRENAS JOAQUIN"/AU
L17           65 "MADRENAS J"/AU OR "MADRENAS JOAQUIN"/AU

=> s l17 and (TCR or T-cell receptor)
           16179 TCR
         3600566 T
         1750104 CELL
          449346 RECEPTOR
           15796 T-CELL RECEPTOR
                    (T(W)CELL(W)RECEPTOR)
L18           28 L17 AND (TCR OR T-CELL RECEPTOR)

=> d l18,cbib,ab,1-28

L18  ANSWER 1 OF 28     MEDLINE on STN
2004047383.    PubMed ID: 14734719.   Lck is required for activation-induced T
     cell death after TCR ligation with partial agonists. Yu Xue-Zhong; Levin
     Steven D; Madrenas Joaquin; Anasetti Claudio. (Human Immunogenetics
     Program, Clinical Research Division, Fred Hutchinson Cancer Research
     Center, Seattle, WA 98109, USA.. xyu@fhcrc.org) . Journal of immunology
     (Baltimore, Md. : 1950), (2004 Feb 1) 172 (3) 1437-43.  Journal code:
     2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB   TCR engagement can induce either T cell proliferation and
     differentiation or activation-induced T cell death (AICD) through
     apoptosis.  The intracellular signaling pathways that dictate such a
     disparate fate after TCR engagement have only been partially elucidated.
     Non-FcR-binding anti-CD3 mAbs induce a partial agonist TCR signaling
     pattern and cause AICD on Ag-activated, cycling T cells.  In this study,
     we examined TCR signaling during the induction of AICD by anti-CD3 fos,
     a non-FcR-binding anti-CD3 mAb.  This mAb activates Fyn, Lck, and
     extracellular signal-regulated kinase, and induces phosphorylation of
     Src-like adapter protein, despite the inability to cause calcium
     mobilization or TCR polarization.  Anti-CD3 fos also fails to
     effectively activate zeta-associated protein of 70 kDa or NF-kappaB.
     Using Ag-specific T cells deficient for Fyn or Lck, we provide compelling
     evidence that activation of Lck is required for the induction of AICD.
     Our data indicate that a selective and distinct TCR signaling pattern is
     required for AICD by TCR partial agonist ligands.
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L18 ANSWER 2 OF 28 MEDLINE on STN
2003605986. PubMed ID: 14688329. Superantigen stimulation reveals the contribution of Lck to negative regulation of T cell activation. Criado Gabriel; **Madrenas Joaquin**. (FOCIS Center for Clinical Immunology and Immunotherapeutics, Robarts Research Institute, 100 Perth Drive, London, Ontario, Canada N6A 5K8.) Journal of immunology (Baltimore, Md. : 1950), (2004 Jan 1) 172 (1) 222-30. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The conventional paradigm of T cell activation through the **TCR** states that Lck plays a critical activating role in this signaling process. However, the T cell response to bacterial superantigens does not require Lck. In this study we report that not only is Lck dispensable for T cell activation by superantigens, but it actively inhibits this signaling pathway. Disruption of Lck function, either by repression of Lck gene expression or by selective pharmacologic inhibitors of Lck, led to increased IL-2 production in response to superantigen stimulation. This negative regulatory effect of Lck on superantigen-induced T cell responses required the kinase activity of Lck and correlated with early **TCR** signaling, but was independent of immunological synapse formation and **TCR** internalization. Our data demonstrate that the multistage role of Lck in T cell signaling includes the activation of a negative regulatory pathway of T cell activation.

L18 ANSWER 3 OF 28 MEDLINE on STN
2003580159. PubMed ID: 12972512. **TCR** subunit specificity of CTLA-4-mediated signaling. Siu Eric; Carreno Beatriz M; **Madrenas Joaquin**. (The FOCIS Centre for Clinical Immunology and Immunotherapeutics, Robarts Research Institute, London, Ontario, Canada N6A 5K8.) Journal of leukocyte biology, (2003 Dec) 74 (6) 1102-7. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB Cytotoxic T-lymphocyte-associated antigen (CTLA)-4 is an activation-induced receptor that down-regulates T cell responses by antagonizing B7-dependent costimulation and/or by transducing a negative signal. The mechanism of CTLA-4-mediated negative signaling is unknown. Recently, it has been postulated that CTLA-4 inhibits T cell activation by causing specific dephosphorylation of the **T cell receptor** (**TCR**)-zeta chain of the antigen-receptor complex through an lck-dependent recruitment of the Src homology-2-containing tyrosine phosphatase-2. To test this hypothesis, we generated stably transfected T cell clones expressing doxycycline-inducible CTLA-4 with CD25:**TCR**-zeta (CD25-zeta) or CD25:CD3-epsilon (CD25-epsilon) fusion proteins. In these clones, ligation of CD25-zeta or of CD25-epsilon with antibodies against CD25 induced full T cell activation, as illustrated by extracellular signal-regulated kinase (ERK) activation and interleukin (IL)-2 production. More importantly, coligation of CTLA-4 with CD25-zeta or of CTLA-4 with CD25-epsilon in the respectively transfected clones inhibited ERK activation and IL-2 production, demonstrating that CTLA-4 does not specifically inhibit signals from **TCR**-zeta but can also inhibit signals from CD3-epsilon. Our results suggest that the target specificity of CTLA-4 is determined by its coligation with any given transmembrane receptor rather than by its intracellular mediators.

L18 ANSWER 4 OF 28 MEDLINE on STN
2003509925. PubMed ID: 14585965. Regulation of T-cell activation by phosphodiesterase 4B2 requires its dynamic redistribution during immunological synapse formation. Arp Jacqueline; Kirchhof Mark G; Baroja Miren L; Nazarian Steven H; Chau Thu A; Strathdee Craig A; Ball Eric H; **Madrenas Joaquin**. (Robarts Research Institute, Department of Microbiology and Immunology, The University of Western Ontario, London, Ontario, Canada N6A 5K8.) Molecular and cellular biology, (2003 Nov) 23 (22) 8042-57. Journal code: 8109087. ISSN: 0270-7306. Pub. country: United States. Language: English.

AB Stimulation of T cells through their antigen receptors (TCRs) causes a transient increase in the intracellular concentration of cyclic AMP

(cAMP). However, sustained high levels of cAMP inhibit T cell responses, suggesting that **TCR** signaling is coordinated with the activation of cyclic nucleotide phosphodiesterases (PDEs). The molecular basis of such a pathway is unknown. Here we show that **TCR**-dependent signaling activates PDE4B2 and that this enhances interleukin-2 production. Such an effect requires the regulatory N terminus of PDE4B2 and correlates with partitioning within lipid rafts, early targeting of this PDE to the immunological synapse, and subsequent accumulation in the antipodal pole of the T cell as activation proceeds.

L18 ANSWER 5 OF 28 MEDLINE on STN

2003193390. PubMed ID: 12705849. A SLAT in the Th2 signalosome. **Madrenas Joaquin**. (The Robarts Research Institute, The University of Western Ontario, London, Canada N6A 5K8.. madrenas@robarts.ca) . Immunity, (2003 Apr) 18 (4) 459-61. Ref: 29. Journal code: 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB There is abundant information on the distinguishing features of **TCR**-mediated signaling in Th1 and Th2 cells. However, the primary signals that determine the commitment and differentiation of naive T cells toward those T helper subsets, especially prior to the contribution of polarizing cytokines, remain elusive. This minireview discusses the potential contribution of SLAT in favoring differentiation along the Th2 lineage and how this may bring us closer to a framework model for Th1/Th2 differentiation.

L18 ANSWER 6 OF 28 MEDLINE on STN

2002325189. PubMed ID: 12067763. Clustering of a lipid-raft associated pool of ERM proteins at the immunological synapse upon **T cell receptor** or CD28 ligation. Tomas Elizabeth M; Chau Thu A; **Madrenas Joaquin**. (The Biotherapeutics, and the Transplantation and Immunobiology Groups, The John P. Robarts Research Institute, Room 2.05, P.O. Box 5015, 100 Perth Drive, London Ont., Canada N6A 5K8.) Immunology letters, (2002 Sep 2) 83 (2) 143-7. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB Although ezrin is tyrosine phosphorylated following **TCR** ligation, its biological role in T cell activation is not known. Here, we shhow that ezrin clusters at the immunological synapse upon T cell stimulation. Clustering of ezrin can be triggered by **TCR** ligation, or, more efficiently, by CD28 ligation. The clusters of ezrin at the immunological synapse include serine/threonine phosphorylated ezrin predominantly located within cell membrane lipid rafts. Based on these data, we propose that ezrin may play a role in the formation/stabilization of lipid raft signalosomes at the immunological synapse and therefore contribute to sustain **TCR**-dependent signalling.

L18 ANSWER 7 OF 28 MEDLINE on STN

2002304703. PubMed ID: 12021313. Surface cytotoxic T lymphocyte-associated antigen 4 partitions within lipid rafts and relocates to the immunological synapse under conditions of inhibition of T cell activation. Darlington Peter J; Baroja Miren L; Chau Thu A; Siu Eric; Ling Vincent; Carreno Beatriz M; **Madrenas Joaquin**. (The Biotherapeutics and Transplantation and Immunobiology Groups, The John P. Robarts Research Institute, and The Departments of Microbiology and Immunology, and Medicine, The University of Western Ontario, London, Ontario N6A 5K8, Canada.) Journal of experimental medicine, (2002 May 20) 195 (10) 1337-47. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB T cell activation through the **T cell receptor** (**TCR**) involves partitioning of receptors into discrete membrane compartments known as lipid rafts, and the formation of an immunological synapse (IS) between the T cell and antigen-presenting cell (APC). Compartmentalization of negative regulators of T cell activation such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is unknown. Recent crystal structures of B7-ligated CTLA-4 suggest that it may form lattices within the IS which could explain the mechanism of action of this molecule. Here, we show that after T cell stimulation, CTLA-4 coclusters with the **TCR** and the lipid raft ganglioside GM1 within the IS. Using subcellular

fractionation, we show that most lipid raft associated CTLA-4 is on the T cell surface. Such compartmentalization is dependent on the cytoplasmic tail of CTLA-4 and can be forced with a glycosylphosphatidylinositol-anchor in CTLA-4. The level of CTLA-4 within lipid rafts increases under conditions of APC-dependent **TCR**-CTLA-4 coligation and T cell inactivation. However, raft localization, although necessary for inhibition of T cell activation, is not sufficient for CTLA-4-mediated negative signaling. These data demonstrate that CTLA-4 within lipid rafts migrates to the IS where it can potentially form lattice structures and inhibit T cell activation.

L18 ANSWER 8 OF 28 MEDLINE on STN

2002263878. PubMed ID: 11994459. Inhibition of CTLA-4 function by the regulatory subunit of serine/threonine phosphatase 2A. Baroja Miren L; Vijayakrishnan Lalitha; Bettelli Estelle; Darlington Peter J; Chau Thu A; Ling Vincent; Collins Mary; Carreno Beatriz M; **Madrenas Joaquin**; Kuchroo Vijay K. (Transplantation and Immunobiology Group, John P. Robarts Research Institute, University of Western Ontario, 100 Perth Drive, London, Ontario N6A 5K8, Canada.) Journal of immunology (Baltimore, Md. : 1950), (2002 May 15) 168 (10) 5070-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The catalytic subunit of the serine/threonine phosphatase 2A (PP2A) can interact with the cytoplasmic tail of CTLA-4. However, the molecular basis and the biological significance of this interaction are unknown. In this study, we report that the regulatory subunit of PP2A (PP2AA) also interacts with the cytoplasmic tail of CTLA-4. Interestingly, **TCR** ligation induces tyrosine phosphorylation of PP2AA and its dissociation from CTLA-4 when coligated. The association between PP2AA and CTLA-4 involves a conserved three-lysine motif in the juxtamembrane portion of the cytoplasmic tail of CTLA-4. Mutations of these lysine residues prevent the binding of PP2AA and enhance the inhibition of IL-2 gene transcription by CTLA-4, indicating that PP2A represses CTLA-4 function. Our data imply that the lysine-rich motif in CTLA-4 may be used to identify small molecules that block its binding to PP2A and act as agonists for CTLA-4 function.

L18 ANSWER 9 OF 28 MEDLINE on STN

2002151014. PubMed ID: 11882031. Thymic re-entry of mature activated T cells and increased negative selection in vascularized allograft recipients. Chau L A; Rohekar S; Wang J-J; Lian D; Chakrabarti S; Zhang L; Zhong R; **Madrenas J**. (Transplantation and Immunobiology Group, John P. Robarts Research Institute, and the Department of Microbiology and Immunology, The University of Western Ontario, London, Ontario, Canada.) Clinical and experimental immunology, (2002 Jan) 127 (1) 43-52. Journal code: 0057202. ISSN: 0009-9104. Pub. country: England: United Kingdom. Language: English.

AB Transplantation tolerance is a dynamic state that involves several homeostatic mechanisms intrinsic to the host. One of these mechanisms is activation-induced T cell death (AICD). However, it is unclear where AICD takes place during alloreactive responses. Since activated T cells can re-enter the thymus, we hypothesized that mature T cells activated by an allograft could be deleted upon re-entry into the thymus. To test this hypothesis, we used wild-type or 2C **TCR** transgenic mice receiving syngeneic or allogeneic heterotopic, vascularized heart grafts. First, we demonstrated that ex vivo CFSE-labelled T cells re-entered the thymus when transferred into allograft recipients but not when transferred into isograft recipients. Next, we compared the changes in cell subset numbers and incidence of apoptosis in the thymi and spleens of allograft or isograft recipients. Seven days after transplantation, at a time in which all the allografts were undergoing rejection, cells expressing donor-MHC class II molecules had migrated to the thymus and to the spleen. In the thymus of allograft recipients, overall cellularity was significantly reduced by 40% and associated with an increase in the number of double negative (CD4-CD8-) thymocytes and a decrease in double positive (CD4+CD8+) thymocytes, consistent with increased negative selection of thymocytes. Additionally, thymi of allograft recipients showed an

increase in the number of recently activated, mature T cells (TCRhi, CD25+, CD44+) and a significant increase in the number of apoptotic cells, especially in the thymic medulla, that involved mature T cells as indicated by the TCRhi, CD44+, CD4 or CD8 single positive phenotype. Spleens of allograft recipients were increased in size and cellularity but did not show any of the changes in cell subsets seen in the thymi. Our data show that after allografting there is an increase in apoptotic cell death that is associated with negative selection of developing thymocytes as well as of alloreactive mature T cells that have re-entered the thymus upon activation in the periphery. This may occur upon migration of graft-derived antigen-presenting cells to the thymus.

L18 ANSWER 10 OF 28 MEDLINE on STN

2001539231. PubMed ID: 11585897. Zap-70-independent Ca(2+) mobilization and Erk activation in Jurkat T cells in response to T-cell antigen receptor ligation. Shan X; Balakir R; Criado G; Wood J S; Seminario M C; **Madrenas J**; Wange R L. (Laboratory of Cellular and Molecular Biology, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224-6825, USA.) Molecular and cellular biology, (2001 Nov) 21 (21) 7137-49. Journal code: 8109087. ISSN: 0270-7306. Pub. country: United States. Language: English.

AB The tyrosine kinase ZAP-70 has been implicated as a critical intermediary between T-cell antigen receptor (**TCR**) stimulation and Erk activation on the basis of the ability of dominant negative ZAP-70 to inhibit **TCR**-stimulated Erk activation, and the reported inability of anti-CD3 antibodies to activate Erk in ZAP-70-negative Jurkat cells. However, Erk is activated in T cells receiving a partial agonist signal, despite failing to activate ZAP-70. This discrepancy led us to reanalyze the ZAP-70-negative Jurkat T-cell line P116 for its ability to support Erk activation in response to **TCR**/CD3 stimulation. Erk was activated by CD3 cross-linking in P116 cells. However, this response required a higher concentration of anti-CD3 antibody and was delayed and transient compared to that in Jurkat T cells. Activation of Raf-1 and MEK-1 was coincident with Erk activation. Remarkably, the time course of Ras activation was comparable in the two cell lines, despite proceeding in the absence of LAT tyrosine phosphorylation in the P116 cells. CD3 stimulation of P116 cells also induced tyrosine phosphorylation of phospholipase C-gamma1 (PLCgamma1) and increased the intracellular Ca(2+) concentration. Protein kinase C (PKC) inhibitors blocked CD3-stimulated Erk activation in P116 cells, while parental Jurkat cells were refractory to PKC inhibition. The physiologic relevance of these signaling events is further supported by the finding of PLCgamma1 tyrosine phosphorylation, Erk activation, and CD69 upregulation in P116 cells on stimulation with superantigen and antigen-presenting cells. These results demonstrate the existence of two pathways leading to **TCR**-stimulated Erk activation in Jurkat T cells: a ZAP-70-independent pathway requiring PKC and a ZAP-70-dependent pathway that is PKC independent.

L18 ANSWER 11 OF 28 MEDLINE on STN

2001251522. PubMed ID: 11349730. HuM291(Nuvion), a humanized Fc receptor-nonbinding antibody against CD3, anergizes peripheral blood T cells as partial agonist of the **T cell receptor**. Chau L A; Tso J Y; Melrose J; **Madrenas J**. (Transplantation and Immunobiology Group, The John P. Robarts Research Institute, London, Ontario, Canada.) Transplantation, (2001 Apr 15) 71 (7) 941-50. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: Humanized Fc receptor (FcR)-nonbinding antibodies against CD3 are promising immunosuppressive agents that may overcome both the neutralizing response to and the cytokine release syndrome seen with conventional monoclonal antibodies against CD3. In addition, evidence from several murine models suggests that these recombinant antibodies may actively induce T cell unresponsiveness by a mechanism other than modulation of the **T cell receptor** (**TCR**) or T cell depletion. We hypothesized that FcR-nonbinding antibodies against CD3 could induce T cell unresponsiveness by acting as partial agonist ligands of the **TCR** and thus, inducing T cell anergy. METHODS: To test this hypothesis, we

examined the signaling and functional effects of HuM291 (Nuvion), a FcR-nonbinding humanized antibody against CD3, on primary human T cells. RESULTS: Short exposure of human peripheral blood T lymphocytes to HuM291 caused a partial agonist type of signaling through the **TCR** characterized by incomplete phosphorylation of **TCR** zeta, failure to activate ZAP-70 and to phosphorylate LAT but activation of ERK-1/-2 and subsequent up-regulation of CD69 expression. These changes correlated with a dose-dependent induction of anergy in human, primary resting T cells, which was reversed by exogenous interleukin-2. CONCLUSIONS: The tolerogenic properties of FcR-nonbinding monoclonal antibodies against CD3 correlate with its ability to reproduce the biochemical and functional effects of **TCR** partial agonist ligands. Thus, generation of engineered antibodies against CD3 with low **TCR** oligomerization potential may provide a clinically applicable partial agonist-based strategy for the prevention of polyclonal T cell responses.

L18 ANSWER 12 OF 28 MEDLINE on STN
2001169354. PubMed ID: 11266941. Generation of partial agonist ligands of the **T-cell receptor** by engineering of antibodies against CD3. Chau L A; Tso J Y; **Madrenas J.** (John P. Robarts Research Institute, University of Western Ontario, London, Ontario, Canada.) Transplantation proceedings, (2001 Feb-Mar) 33 (1-2) 528-9. Journal code: 0243532. ISSN: 0041-1345. Pub. country: United States. Language: English.

L18 ANSWER 13 OF 28 MEDLINE on STN
2001169191. PubMed ID: 11266781. The role of ezrin in **T-cell receptor**-dependent signaling. Tomas E M; Darlington P J; Chau L A; **Madrenas J.** (Transplantation and Immunobiology Group, the John P. Robarts Research Institute, London, Ontario, Canada.) Transplantation proceedings, (2001 Feb-Mar) 33 (1-2) 207-8. Journal code: 0243532. ISSN: 0041-1345. Pub. country: United States. Language: English.

L18 ANSWER 14 OF 28 MEDLINE on STN
2000072728. PubMed ID: 10604992. The inhibitory function of CTLA-4 does not require its tyrosine phosphorylation. Baroja M L; Luxenberg D; Chau T; Ling V; Strathdee C A; Carreno B M; **Madrenas J.** (The John P. Robarts Research Institute, Department of Microbiology and Immunology, University of Western Ontario, London, Canada.) Journal of immunology (Baltimore, Md. : 1950), (2000 Jan 1) 164 (1) 49-55. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB CTLA-4 is a negative regulator of T cell responses. Sequence analysis of this molecule reveals the presence of two cytoplasmic tyrosine residues at positions 165 and 182 that are potential Src homology (SH)-2 domain binding sites. The role of phosphorylation of these residues in CTLA-4-mediated signaling is unknown. Here, we show that sole **TCR** ligation induces zeta-associated protein (ZAP)-70-dependent tyrosine phosphorylation of CTLA-4 that is important for cell surface retention of this molecule. However, CTLA-4 tyrosine phosphorylation is not required for down-regulation of T cell activation following CD3-CTLA-4 coengagement. Specifically, inhibition of extracellular signal-regulated kinase (ERK) activation and of IL-2 production by CTLA-4-mediated signaling occurs in T cells expressing mutant CTLA-4 molecules lacking the cytoplasmic tyrosine residues, and in lck-deficient or ZAP-70-deficient T cells. Therefore, CTLA-4 function involves interplay between two different levels of regulation: phosphotyrosine-dependent cell surface retention and phosphotyrosine-independent association with signaling molecules.

L18 ANSWER 15 OF 28 MEDLINE on STN
1999369986. PubMed ID: 10438919. Phospho-LAT-independent activation of the ras-mitogen-activated protein kinase pathway: a differential recruitment model of **TCR** partial agonist signaling. Chau L A; **Madrenas J.** (Transplantation and Immunobiology Group, John P. Robarts Research Institute, Department of Microbiology, University of Western Ontario, London, Canada.) Journal of immunology (Baltimore, Md. : 1950), (1999 Aug 15) 163 (4) 1853-8. Journal code: 2985117R. ISSN: 0022-1767. Pub.

country: United States. Language: English.

AB Stimulation of mature T cells with agonist ligands of the Ag receptor (**TCR**) causes rapid phosphorylation of tyrosine-based activation motifs in the intracellular portion of **TCR**-zeta and CD3 and activation of several intracellular signaling cascades. Coordinate activation of these pathways is dependent on Lck- and ZAP-70-mediated tyrosine phosphorylation of a 36-kDa linker for activation of T cells and subsequent recruitment of phospholipase C-gamma1, Grb2-SOS, and SLP-76-vav. Here, we show that **TCR** partial agonist ligands can selectively activate one of these pathways, the Ras-mitogen-activated protein kinase pathway, by inducing recruitment of Grb2-SOS complexes to incompletely phosphorylated p21 phospho-**TCR**-zeta. This bypasses the need for activation of Lck and ZAP-70, and for phosphorylation of the linker for activation of T cells to activate Ras. We propose a general model in which differential recruitment of activating complexes away from transmembrane linker proteins may determine selective activation of a given signaling pathway.

L18 ANSWER 16 OF 28 MEDLINE on STN

1999173426. PubMed ID: 10075104. Differential signalling by variant ligands of the **T cell receptor** and the kinetic model of T cell activation. **Madrenas J.** (The John P. Robarts Research Institute, and the Department of Microbiology and Immunology, University of Western Ontario, London, Canada.. madrenas@rri.on.ca) . Life sciences, (1999) 64 (9) 717-31. Ref: 118. Journal code: 0375521. ISSN: 0024-3205. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The structural basis of T cell activation through the **T cell receptor** is still a major unresolved issue in T cell biology. The wealth of information on the generation and structure of **T cell receptor** ligands and the biochemistry of signal transduction from this receptor have been useful in the initial approach to explain how T cell activation occurs. More recently, the generation of variant **T cell receptor** ligands with partial agonist or antagonist properties, the determination of crystal structures for unengaged and engaged T cell receptors, and the kinetics of **T cell receptor** interactions with peptide:MHC molecule complexes have provided new insights on **T cell receptor** function. The common theme arising from these experiments is that the **T cell receptor** is a versatile signalling machine, with an inherent flexibility for ligand recognition that translates in different signalling patterns. Here, I will review the data on differential signalling from the **T cell receptor** upon recognition of partial agonist and antagonist ligands and how these data impact on a more general kinetic model of **T cell receptor**-mediated activation.

L18 ANSWER 17 OF 28 MEDLINE on STN

1999138896. PubMed ID: 9973473. Specific CD3 epsilon association of a phosphodiesterase 4B isoform determines its selective tyrosine phosphorylation after CD3 ligation. Baroja M L; Cieslinski L B; Torphy T J; Wange R L; **Madrenas J.** (Transplantation and Immunobiology Group, John P. Robarts Research Institute, London, Ontario, Canada.) Journal of immunology (Baltimore, Md. : 1950), (1999 Feb 15) 162 (4) 2016-23. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB cAMP-specific phosphodiesterases (PDE) comprise an extensive family of enzymes that control intracellular levels of cAMP and thus regulate T cell responses. It is not known how the function of these enzymes is altered by **TCR** engagement. We have examined this issue by studying one of the PDE isozymes (PDE4B). PDE4B RNA and protein were detected in resting PBLs, and the levels of PDE4B protein increased with cell cycling. In peripheral blood T cells, two previously reported PDE4B isoforms could be detected: one was 75-80 kDa (PDE4B1) and the other was 65-67 kDa (PDE4B2). These two isoforms differed in their N-terminal sequence, with the presence of four potential myristylation sites in the PDE4B2 that are absent in PDE4B1. Consequently, only PDE4B2 was found in association with the CD3var epsilon chain of the **TCR**. In addition, although both isoforms were phosphorylated in tyrosines in pervanadate-stimulated T cells, only the **TCR**-associated PDE4B2 was tyrosine-phosphorylated

following CD3 ligation. The kinetics of phosphorylation of **TCR**-associated PDE4B2 correlated with changes in cAMP levels, suggesting that tyrosine phosphorylation of the **TCR**-associated PDE4B isoform upon engagement of this receptor may be an important regulatory step in PDE4B function. Our results reveal that selectivity of PDE4B activation can be achieved by differential receptor association and phosphorylation of the alternatively spliced forms of this PDE.

L18 ANSWER 18 OF 28 MEDLINE on STN

1999001850. PubMed ID: 9785671. T-cell anergy and altered **T-cell receptor** signaling: effects on autoimmune disease. Salojin K V; Zhang J; **Madrenas J**; Delovitch T L. (Autoimmunity/Diabetes Group, John P. Robarts Research Institute, London, Ontario, Canada.) Immunology today, (1998 Oct) 19 (10) 468-73. Journal code: 8008346. ISSN: 0167-5699. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Immunological self-tolerance can be acquired by several mechanisms, including the induction of anergy in autoreactive T cells. In this sense, anergy is predictably advantageous for the immune system. Here, Konstantin Salojin and colleagues present an alternative view that the induction of anergy in regulatory T cells may be harmful to the host and elicit autoimmune disease.

L18 ANSWER 19 OF 28 MEDLINE on STN

1998252875. PubMed ID: 9584148. Dissociation of intracellular signaling pathways in response to partial agonist ligands of the **T cell receptor**. Chau L A; Bluestone J A; **Madrenas J**. (Transplantation and Immunobiology Group, The John P. Robarts Research Institute, London, Ontario, Canada N6A 5K8.) Journal of experimental medicine, (1998 May 18) 187 (10) 1699-709. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The **T cell receptor** (**TCR**) is a versatile receptor able to generate different signals that result in distinct T cell responses. The pattern of early signals is determined by the **TCR** binding kinetics that control the ability of the ligand to coengage **TCR** and coreceptor. Coengagement of **TCR** and CD4 results in an agonist signaling pattern with complete tyrosine phosphorylation of **TCR** subunits, and recruitment and activation of ZAP-70. In contrast, **TCR** engagement without CD4 coengagement causes a partial agonist type of signaling, characterized by distinct phosphorylation of **TCR** subunits and recruitment but no activation of ZAP-70. The pathways triggered by partial agonist signaling are unknown. Here, we show that agonists cause association of active lck and active ZAP-70 with p120-GTPase-activating protein (p120-GAP). These associations follow engagement of CD4 or CD3, respectively. In contrast, partial agonists do not activate lck or ZAP-70, but induce association of p120-GAP with inactive ZAP-70. Despite these differences, both agonist and partial agonist signals activate the mitogen-activated protein kinase (MAPK) pathway. However, MAPK activation by partial agonists is transient, supporting a kinetic, CD4-dependent model for the mechanism of action of variant **TCR** ligands. Transient MAPK activation may explain some of the responses to **TCR** partial agonists and antagonists.

L18 ANSWER 20 OF 28 MEDLINE on STN

1998137132. PubMed ID: 9476651. Differential signaling through the **T cell receptor**: from biochemistry to transplantation tolerance. **Madrenas J**; Lazarovits A I. (John P. Robarts Research Institute, University of Western Ontario, London, Canada.) Histology and histopathology, (1998 Jan) 13 (1) 221-9. Ref: 70. Journal code: 8609357. ISSN: 0213-3911. Pub. country: Spain. Language: English.

AB Recent advances in our understanding of the structural nature of T cell activation and signal transduction from the **T cell receptor** for antigen make possible the development of new tolerogenic strategies. Here, we summarize the evidence supporting a critical role for the co-receptor molecule (CD4 or CD8) and CD45 in determining the pattern of **T cell receptor**-mediated signaling. The consequences of this differential signaling can range from T cell proliferation and cytokine production to the establishment of a state of proliferative

unresponsiveness known as T cell anergy. Inducing T cell anergy can be an alternative approach for the establishment of transplantation tolerance.

L18 ANSWER 21 OF 28 MEDLINE on STN
97343912. PubMed ID: 9200439. Inactivation of lck and loss of **TCR**-mediated signaling upon persistent engagement with complexes of peptide:MHC molecules. Lee J E; Cossoy M B; Chau L A; Singh B; **Madrenas J**. (The John P. Robarts Research Institute and the Department of Microbiology and Immunology, University of Western Ontario, London, Canada.) Journal of immunology (Baltimore, Md. : 1950), (1997 Jul 1) 159 (1) 61-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB T cell activation follows recognition of specific peptide:MHC molecule complexes in the context of proper costimulation. The earliest detectable event in T cell activation, within seconds of **TCR** ligand recognition, is tyrosine phosphorylation of **TCR** subunits. This causes a cascade of events leading to up-regulation of gene transcription that will drive T cell proliferation and differentiation. Regulation of **TCR**-mediated signaling upon T cell commitment is unclear. Here, we report that persistent stimulation of T cells, beyond 10 min, correlated with a reversible decrease in tyrosine phosphorylation of T cell lysates that did not affect T cell commitment to proliferation. Loss of Ag-induced tyrosine phosphorylation was not due to lack of Ag presentation, loss of **TCR** expression, or T cell death, but, rather, it was associated with a lack of **TCR** subunit tyrosine phosphorylation. We termed this phenomenon **TCR** desensitization by analogy to the loss of signaling observed in other receptor systems upon persistent engagement with agonist ligands. **TCR** desensitization correlated with surface reexpression of **TCR** without concomitant reexpression of coreceptor molecules. Biochemically, **TCR** desensitization correlated with increased levels of serine-phosphorylated lck, loss of lck kinase activity, and reversible loss of cytosolic lck. Thus, **TCR** signaling is regulated by desensitization that may be due to serine phosphorylation of lck causing inactivation and loss of this src kinase. This may have important implications by preventing **TCR** signaling and activation-induced cell death once the T lymphocyte is committed to proliferate.

L18 ANSWER 22 OF 28 MEDLINE on STN
97169064. PubMed ID: 9016871. The efficiency of CD4 recruitment to ligand-engaged **TCR** controls the agonist/partial agonist properties of peptide-MHC molecule ligands. **Madrenas J**; Chau L A; Smith J; Bluestone J A; Germain R N. (Department of Microbiology and Immunology, The University of Western Ontario, London, Canada.) Journal of experimental medicine, (1997 Jan 20) 185 (2) 219-29. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB One hypothesis seeking to explain the signaling and biological properties of **T cell receptor** for antigen (**TCR**) partial agonists and antagonists is the coreceptor density/kinetic model, which proposes that the pharmacologic behavior of a **TCR** ligand is largely determined by the relative rates of (a) dissociation ofligand from an engaged **TCR** and (b) recruitment oflck-linked coreceptors to this ligand-engaged receptor. Using several approaches to prevent or reduce the association of CD4 with occupied **TCR**, we demonstrate that consistent with this hypothesis, the biological and biochemical consequence of limiting this interaction is to convert typical agonists into partial agonist stimuli. Thus, adding anti-CD4 antibody to T cells recognizing a wild-type peptide-MHC class II ligand leads to disproportionate inhibition of interleukin-2 (IL-2) relative to IL-3 production, the same pattern seen using a **TCR** partial agonist/antagonist. In addition, T cells exposed to wild-type ligand in the presence of anti-CD4 antibodies show a pattern of **TCR** signaling resembling that seen using partial agonists, with predominant accumulation of the p21 tyrosine-phosphorylated form of **TCR**-zeta, reduced tyrosine phosphorylation of CD3epsilon, and no detectable phosphorylation of ZAP-70. Similar results are obtained when the wild-type ligand is presented by mutant class II MHC molecules unable to bind CD4. Likewise, antibody coligation of CD3 and CD4 results in an agonist-like

phosphorylation pattern, whereas bivalent engagement of CD3 alone gives a partial agonist-like pattern. Finally, in accord with data showing that partial agonists often induce T cell anergy, CD4 blockade during antigen exposure renders cloned T cells unable to produce IL-2 upon restimulation. These results demonstrate that the biochemical and functional responses to variant **TCR** ligands with partial agonist properties can be largely reproduced by inhibiting recruitment of CD4 to a **TCR** binding a wild-type ligand, consistent with the idea that the relative rates of **TCR**-ligand disengagement and of association of engaged **TCR** with CD4 may play a key role in determining the pharmacologic properties of peptide-MHC molecule ligands. Beyond this insight into signaling through the **TCR**, these results have implications for models of thymocyte selection and the use of anti-coreceptor antibodies in vivo for the establishment ofimmunological tolerance.

L18 ANSWER 23 OF 28 MEDLINE on STN

97077676. PubMed ID: 8920243. Variant **TCR** ligands: new insights into the molecular basis of antigen-dependent signal transduction and T-cell activation. **Madrenas J;** Germain R N. (Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892-1892, USA.) Seminars in immunology, (1996 Apr) 8 (2) 83-101. Ref: 99. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB Recent studies have identified peptide-MHC molecule ligands of alpha beta T-cell receptors with properties apparently distinct from classical agonists. These complexes, which are slight structural variants of the immunizing peptide or original presenting MHC molecule, have several novel properties. They can act as partial agonists able to induce only some and not other effector activities of the T cell, as antagonists able to inhibit T-cell functions stimulated by agonist ligand, or as mixed partial agonists/antagonists. Here we discuss the existing data suggesting that a simple receptor occupancy model does not account for the properties of these **TCR** ligands and review emerging data on qualitative differences in signal transduction following **TCR** engagement by priming versus variant complexes. We propose several non-exclusive models to explain both the biochemical and biological properties of variant ligands with partial agonist or antagonist properties.

L18 ANSWER 24 OF 28 MEDLINE on STN

96382536. PubMed ID: 8790400. Interleukin 2 production, not the pattern of early T-cell antigen receptor-dependent tyrosine phosphorylation, controls anergy induction by both agonists and partial agonists. **Madrenas J;** Schwartz R H; Germain R N. (Lymphocyte Biology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-1892, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1996 Sep 3) 93 (18) 9736-41. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Full activation of T cells requires signaling through the T-cell antigen receptor (**TCR**) and additional surface molecules interacting with ligands on the antigen-presenting cell. **TCR** recognition of agonist ligands in the absence of accessory signals frequently results in the induction of a state of unresponsiveness termed anergy. However, even in the presence of costimulation, anergy can be induced by **TCR** partial agonists. The unique pattern of early receptor-induced tyrosine phosphorylation events induced by partial agonists has led to the hypothesis that altered **TCR** signaling is directly responsible for the development of anergy. Here we show that anergy induction is neither correlated with nor irreversibly determined by the pattern of early **TCR**-induced phosphorylation. Rather, it appears to result from the absence of downstream events related to interleukin 2 receptor occupancy and/or cell division. This implies that the anergic state can be manipulated independently of the precise pattern of early biochemical changes following **TCR** occupancy, a finding with implications for understanding the induction of self-tolerance and the use of partial agonist ligands in the treatment of autoimmune diseases.

L18 ANSWER 25 OF 28 MEDLINE on STN

95125461. PubMed ID: 7824949. Zeta phosphorylation without ZAP-70 activation induced by **TCR** antagonists or partial agonists. **Madrenas J;** Wange R L; Wang J L; Isakov N; Samelson L E; Germain R N. (Lymphocyte Biology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) Science, (1995 Jan 27) 267 (5197) 515-8. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Small changes in the peptide-major histocompatibility complex (MHC) molecule ligands recognized by antigen-specific T cell receptors (TCRs) can convert fully activating complexes into partially activating or even inhibitory ones. This study examined early **TCR**-dependent signals induced by such partial agonists or antagonists. In contrast to typical agonist ligands, both an antagonist and several partial agonists stimulated a distinct pattern of zeta chain phosphorylation and failed to activate associated ZAP-70 kinase. These results identify a specific step in the early tyrosine phosphorylation cascade that is altered after **TCR** engagement with modified peptide-MHC molecule complexes. This finding may explain the different biological responses to **TCR** occupancy by these variant ligands.

L18 ANSWER 26 OF 28 MEDLINE on STN

94366426. PubMed ID: 8084339. Alternatively spliced, germline J alpha 11-2-C alpha mRNAs are the predominant **T cell receptor** alpha transcripts in mouse kidney. **Madrenas J;** Vincent D H; Kriangkum J; Elliott J F; Halloran P F. (Department of Immunology, University of Alberta, Edmonton, Canada.) Molecular immunology, (1994 Sep) 31 (13) 993-1004. Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We recently reported the expression of a truncated **T cell receptor** (**TCR**) alpha mRNA in kidney and brain of normal mice. In the kidney, the truncated **TCR** alpha transcript was expressed by bone marrow-dependent, non-T large interstitial cells located predominantly in the medulla. Here, we report the molecular characterization of the truncated **TCR** alpha transcript from kidney. Using a modified anchored-PCR (A-PCR) technique and directional cloning, 37 cDNA clones extending 5' of the C alpha region were generated. cDNA sequencing showed that 29 of the clones (78%) originated in the J alpha 11-2 region. Of these clones, 17 started upstream or in the J alpha 11-2 exon and contained the entire J alpha 11-2 sequence correctly spliced to the first C alpha exon. Analysis of the sequence revealed the presence of multiple stop codons in all three reading frames. The other 12 clones originated further upstream of the J alpha 11-2 exon and did not include the J alpha 11-2 exon, but rather arose from the joining of a cryptic splice donor signal to the usual **TCR** alpha C splice acceptor. This alternatively spliced transcript contained an open reading frame extending from the upstream J alpha 11-2 region to 82 nucleotides downstream of the beginning of the **TCR** C alpha region, and potentially encoded a 36 amino acid polypeptide. The remaining eight clones all contained the J alpha TA61 region correctly spliced to C alpha with two of these extending upstream of the J alpha TA61 exon. The predominance of J alpha 11-2-C alpha containing clones was confirmed by RNase protection assay using total RNA from kidney and spleen of scid mice. The 3' region of the transcript contained a fully conserved, correctly spliced **TCR** alpha C region which was polyadenylated at the 3' end. The truncated **TCR** alpha mRNA could be detected in preparations of cytoplasmic RNA, indicating that this transcript follows a normal RNA processing pathway. Our results demonstrate that the truncated **TCR** alpha mRNA expressed in normal mouse kidney is a germline J-C transcript resulting from transcription initiated predominantly upstream of the J alpha 11-2 region. This germline transcript in the kidney is undergoing alternative splicing leading to the appearance of an open reading frame coding for a short polypeptide. These results suggest that the product of this transcript may be functionally relevant.

L18 ANSWER 27 OF 28 MEDLINE on STN

92105762. PubMed ID: 1530865. Thymus-independent expression of a truncated

T cell receptor alpha mRNA in murine kidney. **Madrenas J**; Pazderka F; Parfrey N A; Halloran P F. (Department of Medicine, University of Alberta, Edmonton, Canada.) Journal of immunology (Baltimore, Md. : 1950), (1992 Jan 15) 148 (2) 612-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB During studies on gene expression in the kidney, we unexpectedly observed that murine kidney expresses a truncated form of **TCR**-alpha mRNA (1.3-1.4 kb). This transcript was not associated with the presence of complete **TCR**-alpha mRNA (1.7 kb) or detectable **TCR**-beta or -delta transcripts, thus indicating that the truncated **TCR**-alpha mRNA could not be attributed to blood contamination of the kidney RNA preparation. The truncated **TCR**-alpha message appeared to contain at least the C alpha region, as suggested by hybridization with an intra-C alpha 24 oligonucleotide probe, by amplification of the C alpha region with the polymerase chain reaction from total kidney mRNA, and by sequencing of, and hybridization with, the amplified products. In situ hybridization of kidney sections indicated that the transcript was expressed in interstitial cells. Northern blots of cortex and medulla RNA showed that the cells expressing the truncated **TCR**-alpha mRNA were predominantly located in the medulla. To investigate the possibility that the transcript was not produced by T cells or NK cells, fractionation of renal cell suspensions were performed. The truncated **TCR**-alpha mRNA was detected in a fraction containing large (low buoyant density) cells in which no expression of CD3, Thy 1, or NK-1.1 was detected, indicating that these cells are not mature T cells, do not express a functional **TCR**, and are not NK cells. The cells expressing the truncated **TCR**-alpha mRNA were radiosensitive, and were not thymus dependent, because this transcript was as abundant in nude mice as in normal mice. The transcript was not detected in bone marrow. Expression of the truncated **TCR**-alpha mRNA was not dependent on an intact recombinase activity as its expression was not affected by the severe combined immunodeficiency mutation. Our results show that murine kidney contains a population of radiosensitive thymus-independent large interstitial cells that express a truncated **TCR**-alpha mRNA that is not associated with surface expression of functional **TCR**. These cells may have attempted to rearrange **TCR**-alpha genes, suggesting that they may be related to the lymphoid lineage.

L18 ANSWER 28 OF 28 MEDLINE on STN

91118567. PubMed ID: 1703715. Isolation of a murine renal cell population which expresses a truncated **T-cell receptor**-alpha mRNA. **Madrenas J**; Pazderka F; Baergen C; Halloran P F. (Department of Immunology, University of Alberta, Edmonton, Canada.) Transplantation proceedings, (1991 Feb) 23 (1 Pt 1) 837-8. Journal code: 0243532. ISSN: 0041-1345. Pub. country: United States. Language: English.

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(FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
E MARCHALONIS JOHN J/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
E MARCHALONIS J J/IN
L2 5 S E2 OR E3

FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
E MARCHALONIS J J/AU
L3 256 S E2-E5
L4 75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5 4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6 0 S L4 AND (TH1 (W) TH2)

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L7          3660 S (TCR OR T CELL RECEPTOR)
L8          7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9           816 S L8 AND (V BETA)
L10          123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11           39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12           38 S L11 NOT L1

     FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004
L13        24107 S (T CELL RECEPTOR OR TCR)
L14         1326 S L13 AND (TH1 OR TH2 OR T-HELPER 1 OR T-HELPER 2)
L15           18 S L14 AND (ALTERED PEPTIDE LIGANDS)
                 E EVAVOLD B D/AU
L16           33 S E2-E4
                 E MADRENAS J/AU
L17           65 S E3 OR E4
L18           28 S L17 AND (TCR OR T-CELL RECEPTOR)

=> s l14 adn (autoimmun? or immune dysfunction or cytokine dysfunction or cytokine dysregulatio
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         72466 AUTOIMMUN?
        249725 IMMUNE
        112641 DYSFUNCTION
          1070 IMMUNE DYSFUNCTION
                 (IMMUNE(W)DYSFUNCTION)
         60338 CYTOKINE
        112641 DYSFUNCTION
             4 CYTOKINE DYSFUNCTION
                 (CYTOKINE(W)DYSFUNCTION)
         60338 CYTOKINE
          5296 DYSREGULATION
           113 CYTOKINE DYSREGULATION
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                N OR CYTOKINE DYSREGULATION)

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        143822 VACCIN?
        102446 IMMUNIZ?
L20         65 L19 AND (VACCIN? OR IMMUNIZ?)

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L20  ANSWER 1 OF 65     MEDLINE on STN
TI   Fully functional HLA B27-restricted CD4+ as well as CD8+ T cell responses
     in TCR transgenic mice.

L20  ANSWER 2 OF 65     MEDLINE on STN
TI   Epicutaneous immunization with autoantigenic peptides induces T
     suppressor cells that prevent experimental allergic encephalomyelitis.

L20  ANSWER 3 OF 65     MEDLINE on STN
TI   Activation of invariant NKT cells by alphaGalCer administration protects
     mice from MOG35-55-induced EAE: critical roles for administration route
     and IFN-gamma.

L20  ANSWER 4 OF 65     MEDLINE on STN
TI   IL-1 receptor-associated kinase 1 regulates susceptibility to
     organ-specific autoimmunity.

L20  ANSWER 5 OF 65     MEDLINE on STN
TI   Protection against experimental autoimmune encephalomyelitis generated
     by a recombinant adenovirus vector expressing the V beta 8.2 TCR is
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disrupted by coadministration with vectors expressing either IL-4 or IL-10.

L20 ANSWER 6 OF 65 MEDLINE on STN
TI T cell **vaccination** in multiple sclerosis patients with autologous CSF-derived activated T cells: results from a pilot study.

L20 ANSWER 7 OF 65 MEDLINE on STN
TI Targeting autoantigen-specific T cells and suppression of **autoimmune** encephalomyelitis with receptor-modified T lymphocytes.

L20 ANSWER 8 OF 65 MEDLINE on STN
TI Functional plasticity of an antigen-specific memory CD4 T cell population.

L20 ANSWER 9 OF 65 MEDLINE on STN
TI Strategies for designing **vaccines** eliciting **Th1** responses in humans.

L20 ANSWER 10 OF 65 MEDLINE on STN
TI **T cell receptor** transgenic mice recognizing the immunodominant epitope of the Torpedo californica acetylcholine receptor.

L20 ANSWER 11 OF 65 MEDLINE on STN
TI Humanized mice as a model for rheumatoid arthritis.

L20 ANSWER 12 OF 65 MEDLINE on STN
TI Cutting edge: V alpha 14-J alpha 281 NKT cells naturally regulate experimental **autoimmune** encephalomyelitis in nonobese diabetic mice.

L20 ANSWER 13 OF 65 MEDLINE on STN
TI Expression of the tyrosine phosphatase SRC homology 2 domain-containing protein tyrosine phosphatase 1 determines T cell activation threshold and severity of experimental **autoimmune** encephalomyelitis.

L20 ANSWER 14 OF 65 MEDLINE on STN
TI Detection of early changes in **autoimmune** T cell phenotype and function following intravenous administration of type II collagen in a **TCR**-transgenic model.

L20 ANSWER 15 OF 65 MEDLINE on STN
TI Rag-1-dependent cells are necessary for 1,25-dihydroxyvitamin D(3) prevention of experimental **autoimmune** encephalomyelitis.

L20 ANSWER 16 OF 65 MEDLINE on STN
TI **TCR** peptide therapy in human **autoimmune** diseases.

L20 ANSWER 17 OF 65 MEDLINE on STN
TI Impaired Fas signaling pathway is involved in defective T cell apoptosis in **autoimmune** murine arthritis.

L20 ANSWER 18 OF 65 MEDLINE on STN
TI Induction of a type 1 regulatory CD4 T cell response following V beta 8.2 DNA **vaccination** results in immune deviation and protection from experimental **autoimmune** encephalomyelitis.

L20 ANSWER 19 OF 65 MEDLINE on STN
TI Prevention and reversal of experimental **autoimmune** myasthenia gravis by a monoclonal antibody against acetylcholine receptor-specific T cells.

L20 ANSWER 20 OF 65 MEDLINE on STN
TI Two-step activation of T cells, clonal expansion and subsequent **Th1** cytokine production, is essential for the development of clinical **autoimmune** encephalomyelitis.

L20 ANSWER 21 OF 65 MEDLINE on STN
TI Identification of **Th2**-type suppressor T cells among in vivo expanded ocular T cells in mice with experimental **autoimmune** uveoretinitis.

L20 ANSWER 22 OF 65 MEDLINE on STN
TI Repertoire requirements of CD4+ T cells that prevent spontaneous **autoimmune** encephalomyelitis.

L20 ANSWER 23 OF 65 MEDLINE on STN
TI Immunoregulation of encephalitogenic MBP-NAc1-11-reactive T cells by CD4+ **TCR**-specific T cells involves IL-4, IL-10 and IFN-gamma.

L20 ANSWER 24 OF 65 MEDLINE on STN
TI Fulminant spontaneous **autoimmunity** of the central nervous system in mice transgenic for the myelin proteolipid protein-specific **T cell receptor**.

L20 ANSWER 25 OF 65 MEDLINE on STN
TI Intravenous tolerization with type II collagen induces interleukin-4-and interleukin-10-producing CD4+ T cells.

L20 ANSWER 26 OF 65 MEDLINE on STN
TI Reduced chemokine and chemokine receptor expression in spinal cords of **TCR** BV8S2 transgenic mice protected against experimental **autoimmune** encephalomyelitis with BV8S2 protein.

L20 ANSWER 27 OF 65 MEDLINE on STN
TI Characterization and role in experimental systemic lupus erythematosus of T-cell lines specific to peptides based on complementarity-determining region-1 and complementarity-determining region-3 of a pathogenic anti-DNA monoclonal antibody.

L20 ANSWER 28 OF 65 MEDLINE on STN
TI Prevention of diabetes in the NOD mouse by a **Th1** clone specific for a hsp60 peptide.

L20 ANSWER 29 OF 65 MEDLINE on STN
TI Specific **vaccines** against **autoimmune** diseases.

L20 ANSWER 30 OF 65 MEDLINE on STN
TI Animal models of myasthenia gravis.

L20 ANSWER 31 OF 65 MEDLINE on STN
TI Regulation of NOD mouse **autoimmune** diabetes by T cells that recognize a **TCR** CDR3 peptide.

L20 ANSWER 32 OF 65 MEDLINE on STN
TI Evidence for Fas-dependent and Fas-independent mechanisms in the pathogenesis of experimental **autoimmune** encephalomyelitis.

L20 ANSWER 33 OF 65 MEDLINE on STN
TI Androgens alter the cytokine profile and reduce encephalitogenicity of myelin-reactive T cells.

L20 ANSWER 34 OF 65 MEDLINE on STN
TI Induction or protection from experimental **autoimmune** encephalomyelitis depends on the cytokine secretion profile of **TCR** peptide-specific regulatory CD4 T cells.

L20 ANSWER 35 OF 65 MEDLINE on STN
TI Characterization of a peptide analog of a determinant of type II collagen that suppresses collagen-induced arthritis.

L20 ANSWER 36 OF 65 MEDLINE on STN
TI Studies using antigen-presenting cells lacking expression of both B7-1 (CD80) and B7-2 (CD86) show distinct requirements for B7 molecules during priming versus restimulation of **Th2** but not **Th1** cytokine production.

L20 ANSWER 37 OF 65 MEDLINE on STN
TI **Vaccination** with BV8S2 protein amplifies **TCR**-specific regulation and protection against experimental **autoimmune** encephalomyelitis in **TCR**

BV8S2 transgenic mice.

L20 ANSWER 38 OF 65 MEDLINE on STN
TI Novel adjuvants for induction of T-cell and antibody responses to encephalitogenic and regulatory determinants in Lewis rats.

L20 ANSWER 39 OF 65 MEDLINE on STN
TI Suppression of spontaneous uveoretinitis development by non-immunopathogenic peptide **immunization**.

L20 ANSWER 40 OF 65 MEDLINE on STN
TI Effects of **vaccination** with **T cell receptor** peptides: epitope switching to a possible disease-protective determinant of myelin basic protein that is cross-reactive with a **TCR** BV peptide.

L20 ANSWER 41 OF 65 MEDLINE on STN
TI On the role of a possible dialogue between cytokine and **TCR**-presentation mechanisms in the regulation of **autoimmune** disease.

L20 ANSWER 42 OF 65 MEDLINE on STN
TI Neonatal activation of CD28 signaling overcomes T cell anergy and prevents **autoimmune** diabetes by an IL-4-dependent mechanism.

L20 ANSWER 43 OF 65 MEDLINE on STN
TI Immunological tolerance to a pancreatic antigen as a result of local expression of TNFalpha by islet beta cells.

L20 ANSWER 44 OF 65 MEDLINE on STN
TI Autopathogenic T helper cell type 1 (**Th1**) and protective **Th2** clones differ in their recognition of the autoantigenic peptide of myelin proteolipid protein.

L20 ANSWER 45 OF 65 MEDLINE on STN
TI A **T cell receptor** antagonist peptide induces T cells that mediate bystander suppression and prevent **autoimmune** encephalomyelitis induced with multiple myelin antigens.

L20 ANSWER 46 OF 65 MEDLINE on STN
TI Tolerance induction and **autoimmune** encephalomyelitis amelioration after administration of myelin basic protein-derived peptide.

L20 ANSWER 47 OF 65 MEDLINE on STN
TI T cell **vaccination**--induction of anti-idiotypic immune response against **TCR** and shift of **Th1/Th2** balance.

L20 ANSWER 48 OF 65 MEDLINE on STN
TI Triggers of **autoimmune** disease in a murine **TCR**-transgenic model for multiple sclerosis.

L20 ANSWER 49 OF 65 MEDLINE on STN
TI Down-regulation of cell-surface CD4 co-receptor expression and modulation of experimental allergic encephalomyelitis.

L20 ANSWER 50 OF 65 MEDLINE on STN
TI Mechanisms of **autoimmune** disease in the testis and ovary.

L20 ANSWER 51 OF 65 MEDLINE on STN
TI MHC-restriction, cytokine profile, and immunoregulatory effects of human T cells specific for **TCR** V beta CDR2 peptides: comparison with myelin basic protein-specific T cells.

L20 ANSWER 52 OF 65 MEDLINE on STN
TI Treatment of multiple sclerosis with **T-cell receptor** peptides: results of a double-blind pilot trial.

L20 ANSWER 53 OF 65 MEDLINE on STN

TI Effects of **vaccination** against different T cell receptors on maintenance of immune function during murine retrovirus infection.

L20 ANSWER 54 OF 65 MEDLINE on STN
TI Induction of **autoimmunity** in the absence of CD28 costimulation.

L20 ANSWER 55 OF 65 MEDLINE on STN
TI Suppressive **vaccination** with DNA encoding a variable region gene of the **T-cell receptor** prevents **autoimmune** encephalomyelitis and activates **Th2** immunity.

L20 ANSWER 56 OF 65 MEDLINE on STN
TI **T-cell-receptor** dose and the time of treatment during murine retrovirus infection for maintenance of immune function.

L20 ANSWER 57 OF 65 MEDLINE on STN
TI Oral tolerance in myelin basic protein **T-cell receptor** transgenic mice: suppression of **autoimmune** encephalomyelitis and dose-dependent induction of regulatory cells.

L20 ANSWER 58 OF 65 MEDLINE on STN
TI Myelin proteolipid protein-induced **Th1** and **Th2** clones express **TCR** with similar fine specificity for peptide and CDR3 homology despite diverse V beta usage.

L20 ANSWER 59 OF 65 MEDLINE on STN
TI A proteoglycan (aggrecan)-specific T cell hybridoma induces arthritis in BALB/c mice.

L20 ANSWER 60 OF 65 MEDLINE on STN
TI **T cell receptor** V beta complementarity-determining region 1 peptide administration moderates **immune dysfunction** and **cytokine dysregulation** induced by murine retrovirus infection.

L20 ANSWER 61 OF 65 MEDLINE on STN
TI Heterogeneity of autoreactive T cell clones specific for the E2 component of the pyruvate dehydrogenase complex in primary biliary cirrhosis.

L20 ANSWER 62 OF 65 MEDLINE on STN
TI Experimental allergic encephalomyelitis. T cell trafficking to the central nervous system in a resistant Thy-1 congenic mouse strain.

L20 ANSWER 63 OF 65 MEDLINE on STN
TI Induction of T helper cell hyporesponsiveness in an experimental model of **autoimmunity** by using nonmitogenic anti-CD3 monoclonal antibody.

L20 ANSWER 64 OF 65 MEDLINE on STN
TI Collagen-induced arthritis and TCRs in SWR and B10.Q mice expressing an Ek alpha transgene.

L20 ANSWER 65 OF 65 MEDLINE on STN
TI Experimental **autoimmune** orchitis induced by testis and sperm antigen-specific T cell clones: an important pathogenic cytokine is tumor necrosis factor.

=> d l20,cbib,ab,9,16,18,29,40,47,53,60

L20 ANSWER 9 OF 65 MEDLINE on STN
2002393974. PubMed ID: 12141986. Strategies for designing **vaccines** eliciting **Th1** responses in humans. Moingeon P. (Research and Development, Aventis Pasteur, Campus Merieux, 1541 Avenue Marcel Merieux, 69280 Marcy L'Etoile, France.. philippe.moingeon@aventis.com) . Journal of biotechnology, (2002 Sep 25) 98 (2-3) 189-98. Ref: 64. Journal code: 8411927. ISSN: 0168-1656. Pub. country: Netherlands. Language: English.
AB There is currently a major interest in designing **vaccines** capable of

eliciting strong cellular immune responses. The induction of cytotoxic and **Th1** helper cellular responses is for example highly desirable for **vaccines** targeting either chronic infectious diseases or cancers (therapeutic **vaccines**). Similarly, **Th1 vaccines** would be useful in redirecting inappropriate antigen-specific immune responses in patients with **autoimmune** diseases and allergies. Importantly, emerging technologies and a better understanding of the physiology of immune responses offer new avenues to rationally design such **vaccines**. Approaches based on the identification and selection of immunogens containing T cell epitopes can be used, together with epitope-enhancement strategies, to increase binding to MHC, or to improve recognition by **T cell receptor** complexes. Optimized immunogens can subsequently be presented to the immune system with appropriate vectors allowing to target professional antigen-presenting cells, such as dendritic cells. Such antigen presentation platforms can be used alone or in association, as part of mixed **immunization** regimens (heterologous prime-boosts), in order to elicit broad immune responses. The rational design of **Th1** adjuvants can also benefit from our better understanding of the nature of proinflammatory signals leading to the initiation of both innate and adaptive immune effector mechanisms. Candidate **Th1 vaccines** (or components such as vectors or adjuvants) will have to be tested in exploratory clinical studies, implying a need for new assays and methods allowing to assess in a qualitative and quantitative manner low-frequency T cell responses in humans.

L20 ANSWER 16 OF 65 MEDLINE on STN

2001476649. PubMed ID: 11519731. **TCR** peptide therapy in human **autoimmune** diseases. Vandenbark A A; Morgan E; Bartholomew R; Bourdette D; Whitham R; Carlo D; Gold D; Hashim G; Offner H. (Neuroimmunology Research, Veterans Affairs Medical Center, Portland, OR 97201, USA.. vandenbark.arthur_a@portland.va.gov) . Neurochemical research, (2001 Jun) 26 (6) 713-30. Ref: 105. Journal code: 7613461. ISSN: 0364-3190. Pub. country: United States. Language: English.

AB Inflammatory **Th1** cells reacting to tissue/myelin derived antigens likely contribute to the pathogenesis of diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), and psoriasis. One regulatory mechanism that may be useful for treating **autoimmune** diseases involves an innate second set of **Th2** cells specific for portions of the **T cell receptor** of clonally expanded pathogenic **Th1** cells. These **Th2** cells are programmed to respond to internally modified V region peptides from the **T cell receptor** (**TCR**) that are expressed on the **Th1** cell surface in association with major histocompatibility molecules. Once the regulatory **Th2** cells are specifically activated, they may inhibit inflammatory **Th1** cells through a non-specific bystander mechanism. A variety of strategies have been used by us to identify candidate disease-associated **TCR** V genes present on pathogenic **Th1** cells, including BV5S2, BV6S5, and BV13SI in MS, BV3, BV14, and BV17 in RA, and BV3 and BV13S1 in psoriasis. **TCR** peptides corresponding to the mid region of these BV genes were found to be consistently immunogenic in vivo when administered either i.d. in saline or i.m. in incomplete Freund's adjuvant (IFA). In MS patients, repeated injection of low doses of peptides (100-300 microg) significantly boosted the number of **TCR**-reactive **Th2** cells. These activated cells secreted cytokines, including IL-10, that are known to inhibit inflammatory **Th1** cells. Cytokine release could also be induced in **TCR**-reactive **Th2** cells by direct cell-cell contact with **Th1** cells expressing the target V gene. These findings indicate the potential of regulatory **Th2** cells to inhibit not only the target **Th1** cells, but also bystander **Th1** cells expressing different V genes specific for other autoantigens. **TCR** peptide **vaccines** have been used in our studies to treat a total of 171 MS patients (6 trials), 484 RA patients (7 trials), and 177 psoriasis patients (2 trials). Based on this experience in 824 patients with **autoimmune** diseases, **TCR** peptide **vaccination** is safe and well tolerated, and can produce significant clinical improvement in a subset of patients that respond to **immunization**. **TCR** peptide **vaccination** represents a promising approach that is well-suited for treating complex

autoimmune diseases.

L20 ANSWER 18 OF 65 MEDLINE on STN
2001358292. PubMed ID: 11369712. Induction of a type 1 regulatory CD4 T cell response following V beta 8.2 DNA **vaccination** results in immune deviation and protection from experimental **autoimmune** encephalomyelitis. Kumar V; Maglione J; Thatte J; Pederson B; Sercarz E; Ward E S. (Department of Microbiology and Molecular Genetics, University of California, Los Angeles, CA 90095, USA.) International immunology, (2001 Jun) 13 (6) 835-41. Journal code: 8916182. ISSN: 0953-8178. Pub. country: England: United Kingdom. Language: English.

AB DNA **vaccination** has been used to generate effective cellular as well as humoral immunity against target antigens. Here we have investigated the induction and involvement of regulatory T cell (T(reg)) responses in mediating prevention of experimental **autoimmune** encephalomyelitis (EAE), following **vaccination** with plasmid DNA encoding the **TCR** V(beta)8.2 chain predominantly displayed on disease-causing lymphocytes. **Vaccination** with DNA encoding the wild-type **TCR** results in priming of type 1 CD4 T(reg) and skewing of the global response to myelin basic protein in a T(h)2 direction, leading to significant protection from disease. In contrast, **vaccination** with mutant DNA encoding altered residues critically involved in recognition by the T(reg) results in priming of a type 2 regulatory response which fails to mediate immune deviation or protection from EAE. Control mice **immunized** with DNA, encoding **TCR** with changes at an irrelevant site, were protected from antigen-induced disease. Furthermore, protection can be transferred into naive recipients with CD4 T(reg) from wild-type DNA-**immunized** mice but not from animals **vaccinated** with the mutant DNA. These data suggest that **vaccination** with plasmid DNA encoding one or multiple V(beta) genes can be exploited to enhance natural regulatory responses for intervention in **autoimmune** conditions.

L20 ANSWER 29 OF 65 MEDLINE on STN
2000111555. PubMed ID: 10646086. Specific **vaccines** against **autoimmune** diseases. Sela M. (Department of Immunology, Weizmann Institute of Science, Rehovot, Israel.. lisela@weizmann.weizmann.ac.il) . Comptes rendus de l'Academie des sciences. Serie III, Sciences de la vie, (1999 Nov) 322 (11) 933-8. Ref: 30. Journal code: 8503078. ISSN: 0764-4469. Pub. country: France. Language: English.

AB Copolymer 1 (Cop 1, Copaxone) is a synthetic amino acid copolymer effective in suppression of experimental allergic encephalomyelitis (EAE). The suppressive effect of Cop 1 in EAE is not restricted to a certain species, disease type or encephalitogen used for EAE induction. In phase II and III clinical trials, Cop 1 was found to slow the progression of disability and reduce the relapse rate in exacerbating-remitting multiple sclerosis (MS) patients. In vivo and in vitro studies suggest that the mechanism for Cop 1 activity in EAE and MS involves, as an initial step, the binding of Cop 1 to MHC class II molecules. This binding results in competition with myelin antigens for T-cell activation, both at the MHC and **T-cell receptor** levels and in induction of specific suppressor cells of the **Th2** type. As an antigen-specific intervention, Cop 1 has the advantage of reduced probability for long-term damage to the immune system, and is thus a safe and effective novel therapeutic approach to MS. It also serves to illustrate the new concept of a drug/**vaccine** specific for a single **autoimmune** disease. Indeed, we have used a similar approach for myasthenia gravis. Myasthenia gravis (MG) and its experimental animal model, experimental **autoimmune** MG (EAMG), are immune disorders characterized by circulating antibodies and lymphocyte autoreactivity to nicotinic acetylcholine receptor (AChR). We utilized peptides representing different sequences of the human acetylcholine receptor alpha-subunit to study the role of T cells in the initiation, development and immunomodulation of myasthenia gravis. Here we summarize our studies over the last decade on T cells specific to 'myasthenogenic' epitopes of the alpha-subunit of the human acetylcholine receptor and their relevance for myasthenia gravis.

L20 ANSWER 40 OF 65 MEDLINE on STN

1998214396. PubMed ID: 9553780. Effects of **vaccination** with **T cell receptor** peptides: epitope switching to a possible disease-protective determinant of myelin basic protein that is cross-reactive with a **TCR** BV peptide. Vandenbark A A; Chou Y K; Whitham R; Bourdette D N; Offner H. (Research Service, Veterans Affairs Medical Center, Portland, OR 97201, USA.. vandenbark.arthur_a@portland.va.gov) . Immunology and cell biology, (1998 Feb) 76 (1) 83-90. Ref: 26. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB **Immunization** of Lewis rats with guinea-pig myelin basic protein (Gp-MBP) induced T cell responses to primary and secondary encephalitogenic determinants, as well as to a third non-encephalitogenic epitope, residues 55-69. This sequence is of interest due to its protective activity against experimental **autoimmune** encephalomyelitis. Protection involved induction of MBP-55-69-specific T cells expressing cross-reactive **TCR** BV8S6 genes that activated regulatory T cells specific for **TCR** BV8S2 determinants expressed on encephalitogenic T cells. We here present and discuss new evidence suggesting a possible immunological cross-reactivity between the protective Gp-MBP-55-69 peptide and the regulatory BV8S2-39-59 peptide. This cross-reactivity, which may also occur between the human MBP-55-74 peptide and the BV12S2-38-58 sequence, has potentially important implications for human diseases such as multiple sclerosis.

L20 ANSWER 47 OF 65 MEDLINE on STN

97344531. PubMed ID: 9200941. T cell **vaccination**--induction of anti-idiotypic immune response against **TCR** and shift of **Th1/Th2** balance. Kakimoto K; Hara H. (Department of Clinical Investigation, Hara-doi Hospital.) Nippon rinsho. Japanese journal of clinical medicine, (1997 Jun) 55 (6) 1512-8. Ref: 18. Journal code: 0420546. ISSN: 0047-1852. Pub. country: Japan. Language: Japanese.

AB T cell **vaccination**, originally contrived and coinned by I.R. Cohen is the injection of **autoimmune** pathogenic T cell line/clone or **T cell receptor** peptides in an attempt to induce anti-idiotypic regulation to treat **autoimmune** disease. Establishment of many T cell lines/clones from various **autoimmune** animal model and successful injection of these cells as T cell **vaccine** have been reported, although the exact mechanism for **vaccination** effect has not been elucidated. However, recent reports suggest that not the clonal deletion or anergy but the shift of **Th1/Th2** balance of disease-related T lymphocytes may be involved in the effect of **vaccination**.

L20 ANSWER 53 OF 65 MEDLINE on STN

96400439. PubMed ID: 8806815. Effects of **vaccination** against different T cell receptors on maintenance of immune function during murine retrovirus infection. Liang B; Marchalonis J J; Zhang Z; Watson R R. (Department of Family and Community Medicine, University of Arizona, Tucson 85724, USA.) Cellular immunology, (1996 Aug 25) 172 (1) 126-34. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Murine retrovirus infection causes an aberrant stimulation of several subsets of **T helper 2** cells identified by their T cell receptors (**TCR**). C57BL/6 mice were treated with synthetic peptides based upon different human **TCR** V beta CDR1 sequences following experimental infection with the murine retrovirus. Previous studies established that retrovirally infected mice produced autoantibodies to certain of these peptides, and their administration after infection diminished many of the cytokine abnormalities induced by the virus. This study determined whether the complete 16-mer synthetic peptides modeling the V beta CDR1/FR3 were required, and whether admixture of autoantigenic peptides synergized immune preservation. Treatment with complete **TCR** pep beta 3 and pep V beta 5.2 peptide alone and combined largely prevented the retrovirus-induced reduction in B and T cell proliferation and **Th1** cytokine secretion while suppressing excessive production of **Th2** cytokines, which are stimulated by retrovirus infection. Treatment with overlapping short peptides corresponding to the N-terminal 11-mer and C-terminal 12-mer did not significantly prevent the **immune dysfunction** in retrovirus-infected mice. These data suggest that **immune**

dysfunction and abnormal cytokine production, induced by murine retrovirus infection, were largely prevented by **TCR** V beta CDR1 peptides, and the complete CDR1 in association with the five residues from FR2 was required.

L20 ANSWER 60 OF 65 MEDLINE on STN
95363196. PubMed ID: 7636274. **T cell receptor** V beta complementarity-determining region 1 peptide administration moderates **immune dysfunction** and **cytokine dysregulation** induced by murine retrovirus infection. Watson R R; Wang J Y; Dehghanpisheh K; Huang D S; Wood S; Ardestani S K; Liang B; Marchalonis J J. (Department of Family and Community Medicine, University of Arizona College of Medicine, Tucson 85724, USA.) Journal of immunology (Baltimore, Md. : 1950), (1995 Aug 15) 155 (4) 2282-91. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Murine AIDS, induced by LP-BM5 murine leukemia retrovirus infection, causes a progressive and profound immunodeficiency in female C57B1/6 mice. Previously, we reported that autoantibodies were elevated during the initiation phases of this murine retrovirus infection and bound peptide determinants corresponding to CDR1 of several **TCR** V beta-chains. Therefore, we designed studies to determine whether administration of a major **autoimmunogenic TCR** V beta CDR1 peptide before or after infection with LP-BM5 retrovirus would modulate retrovirus-induced dysregulation of T cell function. Administration of the **TCR** V beta CDR1 peptide before murine retrovirus infection significantly prevented its suppression of splenic NK cell activity, T and B cell proliferation, and monokine (IL-6 and TNF-alpha) and **Th1** cytokine (IL-2 and IFN-gamma) release by splenocytes, and inhibited retrovirus-induced elevation of **Th2** cytokine (IL-5 and IL-10). Similar data were obtained with peptide **immunization** 2 wk after murine retrovirus infection at 6 and 16 wk postinfection. However, delaying peptide **immunization** until severe suppression of T and B cell mitogenesis had occurred did not restore their functions. **Immunization** with **TCR** V beta peptide prevents development of retrovirus-induced **immune dysfunction**, which suggests a possible pathogenic role of autoreactive T cells as regulatory elements.

=> d his

(FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
E MARCHALONIS JOHN J/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
E MARCHALONIS J J/IN
L2 5 S E2 OR E3

FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
E MARCHALONIS J J/AU
L3 256 S E2-E5
L4 75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5 4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6 0 S L4 AND (TH1 (W) TH2)

FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7 9668 S (TCR OR T-CELL RECEPTOR)
L8 7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9 816 S L8 AND (V BETA)
L10 123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11 39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12 38 S L11 NOT L1

FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004
L13 24107 S (T CELL RECEPTOR OR TCR)

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L14          1320 S L13 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L15            18 S L14 AND (ALTERED PEPTIDE LIGANDS)
                  E EVAVOLD B D/AU
L16            33 S E2-E4
                  E MADRENAS J/AU
L17            65 S E3 OR E4
L18            28 S L17 AND (TCR OR T-CELL RECEPTOR)
L19           229 S L14 AND (AUTOIMMUN? OR IMMUNE DYSFUNCTION OR CYTOKINE DYSFUNC
L20            65 S L19 AND (VACCIN? OR IMMUNIZ?)

=> s l13 and (TCR peptide? or T-cell receptor peptide? or T-cell receptor polypeptid?)
          16179 TCR
         347611 PEPTIDE?
            169 TCR PEPTIDE?
                  (TCR(W)PEPTIDE?)
        3600566 T
        1750104 CELL
         449346 RECEPTOR
         347611 PEPTIDE?
             90 T-CELL RECEPTOR PEPTIDE?
                  (T(W)CELL(W)RECEPTOR(W)PEPTIDE?)
        3600566 T
        1750104 CELL
         449346 RECEPTOR
          83430 POLYPEPTID?
              6 T-CELL RECEPTOR POLYPEPTID?
                  (T(W)CELL(W)RECEPTOR(W)POLYPEPTID?)
L21           234 L13 AND (TCR PEPTIDE? OR T-CELL RECEPTOR PEPTIDE? OR T-CELL
                  RECEPTOR POLYPEPTID?)

=> s l21 and autoimmun?
          72466 AUTOIMMUN?
L22           92 L21 AND AUTOIMMUN?

=> d l22,ti,1-92

L22  ANSWER 1 OF 92     MEDLINE on STN
TI   Recombinant antibodies with MHC-restricted, peptide-specific, T-cell
     receptor-like specificity: new tools to study antigen presentation and
     TCR-peptide-MHC interactions.

L22  ANSWER 2 OF 92     MEDLINE on STN
TI   Th1/Th2 balance: the hypothesis, its limitations, and implications for
     health and disease.

L22  ANSWER 3 OF 92     MEDLINE on STN
TI   Immunoregulation by Vbeta specific antibodies in myasthenia gravis: mining
     physiological T cell homeostasis for TCR specific therapy.

L22  ANSWER 4 OF 92     MEDLINE on STN
TI   Circulating regulatory anti-T cell receptor antibodies in patients
     with myasthenia gravis.

L22  ANSWER 5 OF 92     MEDLINE on STN
TI   Regulator T cells: specific for antigen and/or antigen receptors?.

L22  ANSWER 6 OF 92     MEDLINE on STN
TI   Complementarity-determining region 3 spectratyping analysis of the TCR
     repertoire in multiple sclerosis.

L22  ANSWER 7 OF 92     MEDLINE on STN
TI   New approaches to dissect degeneracy and specificity in T cell antigen
     recognition.

L22  ANSWER 8 OF 92     MEDLINE on STN
TI   The autoimmune pathogenesis of rheumatoid arthritis: role of
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autoreactive T cells and new immunotherapies.

L22 ANSWER 9 OF 92 MEDLINE on STN
TI **TCR peptide** therapy in human **autoimmune** diseases.

L22 ANSWER 10 OF 92 MEDLINE on STN
TI Kinetics and thermodynamics of **T cell receptor**- autoantigen interactions in murine experimental **autoimmune** encephalomyelitis.

L22 ANSWER 11 OF 92 MEDLINE on STN
TI Nasal application of a naturally processed and presented T cell epitope derived from **TCR** AV11 protects against adjuvant arthritis.

L22 ANSWER 12 OF 92 MEDLINE on STN
TI Clonal restriction of **T-cell receptor** expression by infiltrating lymphocytes in inclusion body myositis persists over time. Studies in repeated muscle biopsies.

L22 ANSWER 13 OF 92 MEDLINE on STN
TI Induction of experimental **autoimmune** arthritis by a public epitope of the **T cell receptor** variable alpha domain of an arthritogenic T cell clone.

L22 ANSWER 14 OF 92 MEDLINE on STN
TI **T cell receptor peptides** for the vaccination therapy of multiple sclerosis.

L22 ANSWER 15 OF 92 MEDLINE on STN
TI Human **TCR** as antigen: homologies and potentially cross-reactive HLA-DR2-restricted epitopes within the AV and BV CDR2 loops.

L22 ANSWER 16 OF 92 MEDLINE on STN
TI Preferential recognition of **TCR** hypervariable regions by human anti-idiotypic T cells induced by T cell vaccination.

L22 ANSWER 17 OF 92 MEDLINE on STN
TI Disruption of positive selection of thymocytes causes **autoimmunity**.

L22 ANSWER 18 OF 92 MEDLINE on STN
TI Treatments targeting the **T cell receptor** (**TCR**): effects of **TCR peptide**-specific T cells on activation, migration, and encephalitogenicity of myelin basic protein-specific T cells.

L22 ANSWER 19 OF 92 MEDLINE on STN
TI The structural basis of T cell activation by superantigens.

L22 ANSWER 20 OF 92 MEDLINE on STN
TI **TCR peptide**-reactive T cells and peripheral tolerance to myelin basic protein.

L22 ANSWER 21 OF 92 MEDLINE on STN
TI Induction or protection from experimental **autoimmune** encephalomyelitis depends on the cytokine secretion profile of **TCR peptide**-specific regulatory CD4 T cells.

L22 ANSWER 22 OF 92 MEDLINE on STN
TI **T cell receptor peptide** vaccination in rheumatoid arthritis: a placebo-controlled trial using a combination of Vbeta3, Vbeta14, and Vbeta17 peptides.

L22 ANSWER 23 OF 92 MEDLINE on STN
TI **T-cell receptor peptide** vaccination in the treatment of rheumatoid arthritis.

L22 ANSWER 24 OF 92 MEDLINE on STN
TI Diversity of the anti-**T-cell receptor** immune response and its

implications for T cell vaccination therapy of multiple sclerosis.

L22 ANSWER 25 OF 92 MEDLINE on STN
TI Effects of vaccination with **T cell receptor peptides**: epitope switching to a possible disease-protective determinant of myelin basic protein that is cross-reactive with a **TCR** BV peptide.

L22 ANSWER 26 OF 92 MEDLINE on STN
TI On the role of a possible dialogue between cytokine and **TCR**-presentation mechanisms in the regulation of **autoimmune** disease.

L22 ANSWER 27 OF 92 MEDLINE on STN
TI Rational approaches to immune regulation.

L22 ANSWER 28 OF 92 MEDLINE on STN
TI **T-cell receptor peptides** as immunotherapy for **autoimmune** disease.

L22 ANSWER 29 OF 92 MEDLINE on STN
TI **TCR peptide** vaccination for **autoimmune** diseases: involvement of T-T interaction between **autoimmune** T cells presenting **TCR peptide** and CD4-CD8- regulatory T cells.

L22 ANSWER 30 OF 92 MEDLINE on STN
TI T cell vaccination--induction of anti-idiotypic immune response against **TCR** and shift of Th1/Th2 balance.

L22 ANSWER 31 OF 92 MEDLINE on STN
TI Regulatory T cells specific for the same framework 3 region of the Vbeta8.2 chain are involved in the control of collagen II-induced arthritis and experimental **autoimmune** encephalomyelitis.

L22 ANSWER 32 OF 92 MEDLINE on STN
TI Modulation of experimental allergic encephalomyelitis in mice by immunization with a peptide specific for the gamma delta **T cell receptor**.

L22 ANSWER 33 OF 92 MEDLINE on STN
TI Definition of an extended MHC class II-peptide binding motif for the **autoimmune** disease-associated Lewis rat RT1.BL molecule.

L22 ANSWER 34 OF 92 MEDLINE on STN
TI Inactivation of **T cell receptor peptide**-specific CD4 regulatory T cells induces chronic experimental **autoimmune** encephalomyelitis (EAE).

L22 ANSWER 35 OF 92 MEDLINE on STN
TI MHC-restriction, cytokine profile, and immunoregulatory effects of human T cells specific for **TCR** V beta CDR2 peptides: comparison with myelin basic protein-specific T cells.

L22 ANSWER 36 OF 92 MEDLINE on STN
TI An alpha-chain **TCR** CDR3 peptide can enhance EAE induced by myelin basic protein or proteolipid protein.

L22 ANSWER 37 OF 92 MEDLINE on STN
TI Treatment of multiple sclerosis with **T-cell receptor peptides**: results of a double-blind pilot trial.

L22 ANSWER 38 OF 92 MEDLINE on STN
TI T-T cellular interaction between CD4-CD8- regulatory T cells and T cell clones presenting **TCR peptide**. Its implication for **TCR** vaccination against experimental **autoimmune** encephalomyelitis.

L22 ANSWER 39 OF 92 MEDLINE on STN
TI **T cell receptor peptides** in treatment of **autoimmune** disease: rationale and potential.

L22 ANSWER 40 OF 92 MEDLINE on STN

TI The development and use of **T cell receptor peptide** vaccines.

L22 ANSWER 41 OF 92 MEDLINE on STN
TI Autoregulation of **Tcr** V region epitopes in **autoimmune** disease.

L22 ANSWER 42 OF 92 MEDLINE on STN
TI Autoantibodies against peptide-defined epitopes of T-cell receptors in retrovirally infected humans and mice.

L22 ANSWER 43 OF 92 MEDLINE on STN
TI Pretreatment with **T cell receptor peptides** using a conventional immunization protocol does not induce effective protection against **autoimmune** encephalomyelitis.

L22 ANSWER 44 OF 92 MEDLINE on STN
TI Anti-**T-cell receptor peptide** specific T-cells and adjuvant arthritis.

L22 ANSWER 45 OF 92 MEDLINE on STN
TI **T cell receptor peptide** vaccines as immunotherapy.

L22 ANSWER 46 OF 92 MEDLINE on STN
TI Down-regulation of class II major histocompatibility complex molecules on antigen presenting cells after interaction with helper T cells.

L22 ANSWER 47 OF 92 MEDLINE on STN
TI Regulation of **autoimmune** response.

L22 ANSWER 48 OF 92 MEDLINE on STN
TI Limited regulatory effect of **T cell receptor**-derived peptides.

L22 ANSWER 49 OF 92 MEDLINE on STN
TI A self-reactive class I-restricted T-cell response of H-2b mice to determinants of the V beta 8.2 domain of the **T-cell receptor** for antigen.

L22 ANSWER 50 OF 92 MEDLINE on STN
TI Immunodominant framework region 3 peptide from **TCR** V beta 8.2 chain controls murine experimental **autoimmune** encephalomyelitis.

L22 ANSWER 51 OF 92 MEDLINE on STN
TI Regulatory T cell network.

L22 ANSWER 52 OF 92 MEDLINE on STN
TI Autoantibodies to the alpha/beta T-cell receptors in human immunodeficiency virus infection: dysregulation and mimicry.

L22 ANSWER 53 OF 92 MEDLINE on STN
TI Coculture of **TCR peptide**-specific T cells with basic protein-specific T cells inhibits proliferation, IL-3 mRNA, and transfer of experimental **autoimmune** encephalomyelitis.

L22 ANSWER 54 OF 92 MEDLINE on STN
TI Immunity to **T cell receptor peptides**: theory and applications.

L22 ANSWER 55 OF 92 MEDLINE on STN
TI Definition of encephalitogenic and immunodominant epitopes of guinea pig myelin basic protein (Gp-BP) in Lewis rats tolerized neonatally with Gp-BP or Gp-BP peptides.

L22 ANSWER 56 OF 92 MEDLINE on STN
TI CDR1 **T-cell receptor** beta-chain peptide induces major histocompatibility complex class II-restricted T-T cell interactions.

L22 ANSWER 57 OF 92 MEDLINE on STN
TI Antigen analogs/MHC complexes as specific **T cell receptor** antagonists.

L22 ANSWER 58 OF 92 MEDLINE on STN

TI Immunity to **TCR peptides** in multiple sclerosis. II. T cell recognition of V beta 5.2 and V beta 6.1 CDR2 peptides.

L22 ANSWER 59 OF 92 MEDLINE on STN
TI Immunity to **TCR peptides** in multiple sclerosis. I. Successful immunization of patients with synthetic V beta 5.2 and V beta 6.1 CDR2 peptides.

L22 ANSWER 60 OF 92 MEDLINE on STN
TI **T cell receptor peptide** therapy for **autoimmune** encephalomyelitis: stronger immunization is necessary for effective vaccination.

L22 ANSWER 61 OF 92 MEDLINE on STN
TI Modulation of EAE by vaccination with **T cell receptor peptides**: V beta 8 **T cell receptor peptide**-specific CD4+ lack direct immunoregulatory activity.

L22 ANSWER 62 OF 92 MEDLINE on STN
TI Modulation of EAE by vaccination with **T cell receptor peptides**: V beta 8 **T cell receptor peptide**-specific CD4+ lymphocytes lack direct immunoregulatory activity.

L22 ANSWER 63 OF 92 MEDLINE on STN
TI The effect of **TCR** V beta 8 peptide protection and therapy on T cell populations isolated from the spinal cords of Lewis rats with experimental **autoimmune** encephalomyelitis.

L22 ANSWER 64 OF 92 MEDLINE on STN
TI The involvement of **T cell receptor peptide**-specific regulatory CD4+ T cells in recovery from antigen-induced **autoimmune** disease.

L22 ANSWER 65 OF 92 MEDLINE on STN
TI Modulation of EAE by vaccination with **T cell receptor peptides**: V beta 8 **T cell receptor peptide**-specific CD4+ lymphocytes lack direct immunoregulatory activity.

L22 ANSWER 66 OF 92 MEDLINE on STN
TI Where, when, and how to detect biased expression of disease-relevant V beta genes in rats with experimental **autoimmune** encephalomyelitis.

L22 ANSWER 67 OF 92 MEDLINE on STN
TI **T-cell receptor peptide** therapy in EAE and MS.

L22 ANSWER 68 OF 92 MEDLINE on STN
TI Treatment of relapsing experimental **autoimmune** encephalomyelitis with **T cell receptor peptides**.

L22 ANSWER 69 OF 92 MEDLINE on STN
TI **TCR peptide** therapy in **autoimmune** diseases.

L22 ANSWER 70 OF 92 MEDLINE on STN
TI Vaccination with **T-cell receptor peptides**.

L22 ANSWER 71 OF 92 MEDLINE on STN
TI Human T cell **autoimmunity** against myelin basic protein: CD4+ cells recognizing epitopes of the **T cell receptor** beta chain from a myelin basic protein-specific T cell clone.

L22 ANSWER 72 OF 92 MEDLINE on STN
TI Requirement for CD8+ cells in **T cell receptor peptide**-induced clonal unresponsiveness.

L22 ANSWER 73 OF 92 MEDLINE on STN
TI New approaches to the therapy of **autoimmune** diseases: rheumatoid arthritis as a paradigm.

L22 ANSWER 74 OF 92 MEDLINE on STN
TI Spontaneous development of protective anti-**T cell receptor autoimmunity** targeted against a natural EAE-regulatory idiotope located within the 39-59 region of the **TCR**-V beta 8.2 chain.

L22 ANSWER 75 OF 92 MEDLINE on STN
TI Management of early inflammatory arthritis. Intervention with immunomodulatory agents: T cell vaccination.

L22 ANSWER 76 OF 92 MEDLINE on STN
TI **T cell receptor peptide** therapy for **autoimmune** disease.

L22 ANSWER 77 OF 92 MEDLINE on STN
TI **TCR peptide** therapy decreases the frequency of encephalitogenic T cells in the periphery and the central nervous system.

L22 ANSWER 78 OF 92 MEDLINE on STN
TI Common sequence on distinct V beta genes defines a protective idiotope in experimental encephalomyelitis.

L22 ANSWER 79 OF 92 MEDLINE on STN
TI The human **T cell receptor** in health and disease.

L22 ANSWER 80 OF 92 MEDLINE on STN
TI Human autoantibodies reactive with synthetic autoantigens from **T-cell receptor** beta chain.

L22 ANSWER 81 OF 92 MEDLINE on STN
TI Studies of V beta 8 **T cell receptor peptide** treatment in experimental **autoimmune** encephalomyelitis.

L22 ANSWER 82 OF 92 MEDLINE on STN
TI Characterization of the immune response to a secondary encephalitogenic epitope of basic protein in Lewis rats. I. **T cell receptor peptide** regulation of T cell clones expressing cross-reactive V beta genes.

L22 ANSWER 83 OF 92 MEDLINE on STN
TI Immunoregulation of **autoimmune** disease by vaccination with **T cell receptor peptides**.

L22 ANSWER 84 OF 92 MEDLINE on STN
TI T cell receptors, immunoregulation, and **autoimmunity**.

L22 ANSWER 85 OF 92 MEDLINE on STN
TI Trials of vaccination against experimental **autoimmune** uveoretinitis with a **T-cell receptor peptide**.

L22 ANSWER 86 OF 92 MEDLINE on STN
TI **T-cell receptor peptide** immunization leads to enhanced and chronic experimental allergic encephalomyelitis.

L22 ANSWER 87 OF 92 MEDLINE on STN
TI Immunization with **T cell receptor peptides**.

L22 ANSWER 88 OF 92 MEDLINE on STN
TI Antibodies against **T-cell receptor peptide** arrest **autoimmune** rejection of normal central nervous system myelin.

L22 ANSWER 89 OF 92 MEDLINE on STN
TI **T cell receptor peptide** therapy triggers autoregulation of experimental encephalomyelitis.

L22 ANSWER 90 OF 92 MEDLINE on STN
TI Antibodies specific for VB8 receptor peptide suppress experimental **autoimmune** encephalomyelitis.

L22 ANSWER 91 OF 92 MEDLINE on STN
TI Vaccination against experimental allergic encephalomyelitis with **T cell receptor peptides.**

L22 ANSWER 92 OF 92 MEDLINE on STN
TI **T-cell receptor** genes in **autoimmune** mice: T-cell subsets have unexpected **T-cell receptor** gene programs.

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L22 ANSWER 2 OF 92 MEDLINE on STN
2003407533. PubMed ID: 12946237. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. Kidd Parris. Alternative medicine review : a journal of clinical therapeutic, (2003 Aug) 8 (3) 223-46. Ref: 95. Journal code: 9705340. ISSN: 1089-5159. Pub. country: United States. Language: English.
AB One theory of immune regulation involves homeostasis between T-helper 1 (Th1) and T-helper 2 (Th2) activity. The Th1/Th2 hypothesis arose from 1986 research suggesting mouse T-helper cells expressed differing cytokine patterns. This hypothesis was adapted to human immunity, with Th1- and Th2-helper cells directing different immune response pathways. Th1 cells drive the type-1 pathway ("cellular immunity") to fight viruses and other intracellular pathogens, eliminate cancerous cells, and stimulate delayed-type hypersensitivity (DTH) skin reactions. Th2 cells drive the type-2 pathway ("humoral immunity") and up-regulate antibody production to fight extracellular organisms; type 2 dominance is credited with tolerance of xenografts and of the fetus during pregnancy. Overactivation of either pattern can cause disease, and either pathway can down-regulate the other. But the hypothesis has major inconsistencies; human cytokine activities rarely fall into exclusive pro-Th1 or -Th2 patterns. The non-helper regulatory T cells, or the antigen-presenting cells (APC), likely influence immunity in a manner comparable to Th1 and Th2 cells. Many diseases previously classified as Th1 or Th2 dominant fail to meet the set criteria. Experimentally, Th1 polarization is readily transformed to Th2 dominance through depletion of intracellular glutathione, and vice versa. Mercury depletes glutathione and polarizes toward Th2 dominance. Several nutrients and hormones measurably influence Th1/Th2 balance, including plant sterols/sterolins, melatonin, probiotics, progesterone, and the minerals selenium and zinc. The long-chain omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) significantly benefit diverse inflammatory and **autoimmune** conditions without any specific Th1/Th2 effect. Th1/Th2-based immunotherapies, e.g., **T-cell receptor** (**TCR**) **peptides** and interleukin-4 (IL-4) injections, have produced mixed results to date.

L22 ANSWER 5 OF 92 MEDLINE on STN
2003231994. PubMed ID: 12753496. Regulator T cells: specific for antigen and/or antigen receptors?. Rubin B; de Durana Y Diaz; Li N; Sercarz E E. (La Jolla Institute for Allergy and Immunology, Division of Immune Regulation, San Diego, CA, USA.. rubin@immgen.cnrs.fr) . Scandinavian journal of immunology, (2003 May) 57 (5) 399-409. Ref: 60. Journal code: 0323767. ISSN: 0300-9475. Pub. country: England: United Kingdom. Language: English.
AB Adaptive immune responses are regulated by many different molecular and cellular effectors. Regulator T cells are coming to their rights again, and these T cells seem to have ordinary alpha/beta T-cell receptors (TCRs) and to develop in the thymus. **Autoimmune** responses are tightly regulated by such regulatory T cells, a phenomenon which is beneficial to the host in **autoimmune** situations. However, the regulation of **autoimmune** responses to tumour cells is harmful to the host, as this regulation delays the defence against the outgrowth of neoplastic cells. In the present review, we discuss whether regulatory T cells are specific for antigen and/or for antigen receptors. Our interest in these phenomena comes from the findings that T cells produce many more **TCR**-alpha and

TCR beta chains than are necessary for surface membrane expression of **TCR**-alphabeta heterodimers with CD3 complexes. Excess **TCR** chains are degraded by the proteasomes, and **TCR peptides** thus become available to the assembly pathway of major histocompatibility complex class I molecules. Consequently, do T cells express two different identification markers on the cell membrane, the **TCR**-alphabeta clonotype for recognition by B-cell receptors and clonotypic **TCR**-alphabeta peptides for recognition by T cells?

L22 ANSWER 26 OF 92 MEDLINE on STN
1998199266. PubMed ID: 9538464. On the role of a possible dialogue between cytokine and **TCR**-presentation mechanisms in the regulation of **autoimmune** disease. Bar-Or R L; Segel L A. (Department of Applied Mathematics and Computer Science, Weizmann Institute of Science, Rehovot, Israel.) Journal of theoretical biology, (1998 Jan 21) 190 (2) 161-78. Journal code: 0376342. ISSN: 0022-5193. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Autoimmune** diseases are thought to occur through some weakness in an active process of autoregulation. Two different regulatory mechanisms have been proposed separately during the years: a "non-specific" mechanism, via Th1-Th2 non-specific cytokines, and a "specific" one-on-one mechanism, via presentation of peptides, i.e., **T cell receptor (TCR) peptides**, by the T cells themselves. Several anti-idiotypic models rely on the latter to explain the effects of "T-cell-vaccination" therapy. We present and analyse a model for the interaction between both regulatory mechanisms within an ensemble composed of Th1 and Th2 cells. Our model shows how both **TCR** presentation and non-specific Th1/2 signals can cooperate in the choice of the prevailing Th1 or Th2 response. We show how **TCR** presentation can foster regulation, without necessitating a particular "suppressor" agent, of the type that some have assumed to play a central role in the regulation of **autoimmunity**. Our results suggest an important role for the cells' sensitivities to Th1 and Th2 derived cytokines; only for certain sensitivity ranges, is it possible to switch dominance between subtypes. It is argued that memory is sustained via modulation of sensitivities to cytokines, not only to antigens. The results and hypotheses also suggest one possible reason for the known correlation between standard and **autoimmune** diseases. Several therapies and informative experiments are suggested. We argue, for example, that administering a non-relevant peptide while increasing the ratio between the clones reactive to it and other clones in the pancreas, might cure **autoimmune** diabetes. Moreover, we predict that disease could be prevented by administering an **autoimmune** peptide at an early age while forcing the system to react in a Th2 fashion.

L22 ANSWER 27 OF 92 MEDLINE on STN
1998140208. PubMed ID: 9479581. Rational approaches to immune regulation. Paterson Y. (Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, USA.. yvonne@mail.med.upenn.edu) . Immunologic research, (1998) 17 (1-2) 191-207. Ref: 96. Journal code: 8611087. ISSN: 0257-277X. Pub. country: United States. Language: English.

AB Our studies are mainly focused on developing strategies of immune regulation. In the case of infectious and neoplastic disease, our approach is to upregulate cell-mediated immunity to viral of tumor antigens using an intracellular bacterium as a vector for targeting these antigens to the major histocompatibility complex (MHC) class I and class II pathways of antigen processing, in addition to exploiting the adjuvant properties of the vector to stimulate innate immunity. In the area of **autoimmunity**, we are attempting to downregulate the immune response by specific immune intervention directed against autoreactive T cells. In these studies we use murine models for multiple sclerosis. Our approach is to use both rationally designed **T cell receptor (TCR) peptide** analogs and recombinant viral vectors that express **TCR** components to regulate the disease.

L22 ANSWER 28 OF 92 MEDLINE on STN
1998080707. PubMed ID: 9419437. **T-cell receptor peptides** as

immunotherapy for **autoimmune** disease. Gold D P; Shroeder K; Golding A; Brostoff S W; Wilson D B. (Sidney Kimmel Cancer Center, San Diego, CA 92121, USA.) Critical reviews in immunology, (1997) 17 (5-6) 507-10. Ref: 24. Journal code: 8914819. ISSN: 1040-8401. Pub. country: United States. Language: English.

AB The observations in both mouse and rat models of experimental allergic encephalomyelitis (EAE) demonstrating restricted **T-cell receptor** (**TCR**) usage among pathogenic T cells has led to the generation of a new class of therapeutic vaccines composed of **TCR** V region peptides. Whether a similar approach will be of use in the treatment of human **autoimmune** disorders is still unclear. The experiments performed in our laboratory over the past several years have focused on two aspects of **TCR peptide** immunoregulation, namely, (1) how to identify the critical T-cell populations involved in the pathology of **autoimmune** disease, and (2) how to identify biologically relevant **TCR peptides**--those endogenous **TCR peptides** presented in association with MHC molecules on the surface of pathogenic T cells that are recognized by immunoregulatory T-cell populations. Results of our recently completed clinical studies regarding **TCR** V beta expression among CD4+ T cells in the cerebral spinal fluid (CSF) of patients with multiple sclerosis suggests that these cells may be an appropriate T-cell population to be targeted for **TCR peptide** therapy. In addition, our studies on the immune response to autologous, soluble **TCR** heterodimers may provide a strategy for the identification of new **TCR peptide** candidate vaccines.

L22 ANSWER 29 OF 92 MEDLINE on STN

97344532. PubMed ID: 9200942. **TCR peptide** vaccination for **autoimmune** diseases: involvement of T-T interaction between **autoimmune** T cells presenting **TCR peptide** and CD4-CD8- regulatory T cells. Yamamura T. Nippon rinsho. Japanese journal of clinical medicine, (1997 Jun) 55 (6) 1519-24. Ref: 14. Journal code: 0420546. ISSN: 0047-1852. Pub. country: Japan. Language: Japanese.

AB **TCR peptide** vaccination has been recently regarded as a future therapy for **autoimmune** diseases. In spite of the potential value, its underlying mechanisms have not been clearly established. M. F. Kozovska, T. Tabira and I have recently analyzed the immune regulation triggered by V beta 17a-50-68 peptide vaccine in SJL/J mice and desciribed a novel T-T interaction between encephalitogenic T cells presenting **TCR peptide** and CD4-CD8- regulatory T cells (Journal of Immunology 157:1781, 1996). In this brief review, I discuss how anti-idiotypic regulation can be triggered by the exogenous **TCR peptide**, and what we have learned from the animal experiments with regard to the natural regulation in human **autoimmune** diseases such as multiple sclerosis.

L22 ANSWER 30 OF 92 MEDLINE on STN

97344531. PubMed ID: 9200941. T cell vaccination--induction of anti-idiotypic immune response against **TCR** and shift of Th1/Th2 balance. Kakimoto K; Hara H. (Department of Clinical Investigation, Hara-doi Hospital.) Nippon rinsho. Japanese journal of clinical medicine, (1997 Jun) 55 (6) 1512-8. Ref: 18. Journal code: 0420546. ISSN: 0047-1852. Pub. country: Japan. Language: Japanese.

AB T cell vaccination, originally contrived and coinned by I.R. Cohen is the injection of **autoimmune** pathogenic T cell line/clone or **T cell receptor peptides** in an attempt to induce anti-idiotypic regulation to treat **autoimmune** disease. Establishment of many T cell lines/clones from various **autoimmune** animal model and successful injection of these cells as T cell vaccine have been reported, although the exact mechanism for vaccination effect has not been elucidated. However, recent reports suggest that not the clonal deletion or anergy but the shift of Th1/Th2 balance of disease-related T lymphocytes may be involved in the effect of vaccination.

L22 ANSWER 39 OF 92 MEDLINE on STN

96234783. PubMed ID: 8699526. **T cell receptor peptides** in treatment of **autoimmune** disease: rationale and potential. Vandenbark A A; Hashim G A; Offner H. (Veterans Affairs Medical Center, New York, New

York, USA.) Journal of neuroscience research, (1996 Feb 15) 45 (4) 391-402. Ref: 80. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB The natural tendency in T cell-mediated **autoimmune** conditions to develop focused antigen-specific responses that over-utilize certain **T cell receptor** (**TCR**) V region segments prompts the induction of anti-**TCR**-specific T cells and antibodies that can inhibit the pathogenic T cells and promote recovery from disease. This natural regulatory network can be manipulated by injecting synthetic peptide vaccines that correspond to segments of the over-expressed V genes. In experimental **autoimmune** encephalomyelitis (EAE), an animal model for the human disease multiple sclerosis (MS), the pathogenic T cells are directed at myelin components, including basic protein (MBP). In some strains such as the Lewis rat and the PL/J mouse, the encephalitogenic BP-specific T cells overexpress a particular V region gene (V beta 8.2) in the **TCR**. In vivo administration of V beta 8.2 peptides in rats or mice can prevent and treat EAE by boosting regulatory anti-V beta 8.2-specific T cells that inhibit but do not delete the encephalitogenic specificities. This regulation is mediated by soluble factors, suggesting that the presence of regulatory **TCR**-specific T cells within the target organ (the central nervous system) may inhibit not only the stimulating V beta 8.2 + T cells, but also bystander T cells bearing different V genes. Parallel studies in MS patients have revealed striking V gene biases among BP-specific T cell clones from some patients that provided a rationale for **TCR peptide** therapy. Injection of V beta 5.2 and V beta 6.1 peptides boosted the frequency of **TCR peptide**-specific T cells and reduced responses to BP, in some cases with clinical benefit, indicating the presence of an anti-**TCR** regulatory network in humans that may also be manipulated with **TCR peptide** therapy.

L22 ANSWER 40 OF 92 MEDLINE on STN

96229159. PubMed ID: 8644509. The development and use of **T cell receptor peptide** vaccines. Brostoff S. (Immune Response Corporation, Carlsbad, California 92008, USA.) Advances in experimental medicine and biology, (1995) 383 249-54. Ref: 18. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

L22 ANSWER 41 OF 92 MEDLINE on STN

96229157. PubMed ID: 8644507. Autoregulation of **Tcr** V region epitopes in **autoimmune** disease. Schluter S F; Wang E; Winfield J B; Yocum D E; Marchalonis J J. (College of Medicine, University of Arizona, Tucson 85724, USA.) Advances in experimental medicine and biology, (1995) 383 231-6. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

AB Normal individuals possess low levels of autoantibodies specific for certain peptide defined regions of **T-cell receptor** (**Tcr**) variable regions, particularly CDR1 and Fr3. These regions are predicted to be exposed on the surface of the native molecule and, by analogy and comparison with immunoglobulins, correspond to public idiotype determinants. The anti-**Tcr** idiotype antibodies appear to be ubiquitous and we propose that they play a role in the regulation of T-cell function. To delineate the parameters of expression of these antibodies, we characterized anti-**Tcr** antibody activity in normal individuals, in those suffering from the **autoimmune** diseases rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and in patients with non-**autoimmune** arthritis (osteoarthritis) as a disease control. There were significant increases in autoantibody levels in the **autoimmune** patients. There was also variation in isotype and the particular variable regions recognized. IgM autoantibodies directed against a few peptide defined determinants were elevated in RA, whereas SLE patient sera showed high levels of IgG binding to a broad spectrum of **Tcr peptides**.

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"HELP COMMANDS" at an arrow prompt (=>).

=> d l22,cbib,ab,45,47,48,51,54,56,59,60,64,70,79

L22 ANSWER 45 OF 92 MEDLINE on STN
95305028. PubMed ID: 7785503. **T cell receptor peptide** vaccines as immunotherapy. Brostoff S W. (Immune Response Corporation, Carlsbad, CA 92008, USA.) Agents and actions. Supplements, (1995) 47 53-8. Ref: 18. Journal code: 7801014. ISSN: 0379-0363. Pub. country: Switzerland. Language: English.

L22 ANSWER 47 OF 92 MEDLINE on STN
95226015. PubMed ID: 7710719. Regulation of **autoimmune** response. Ridgway W M; Weiner H L; Fathman C G. (Department of Medicine, Stanford University School of Medicine, California 94305.) Current opinion in immunology, (1994 Dec) 6 (6) 946-55. Ref: 51. Journal code: 8900118. ISSN: 0952-7915. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Recent work on such apparently disparate fields as **T-cell receptor peptide**-induced regulation, superantigens, antigen-induced tolerance, models of peripheral tolerance, apoptosis, and **T-cell receptor** antagonists demonstrates a similarity in immune response from a regulatory perspective. In many systems, a 'tolerance' pathway is observed, characterized broadly as an initial disturbance in the immune system, with a resulting predominance of effector cells, followed by a homeostatic response (often requiring CD8+ cells) which leads the effector population into **T-cell receptor** downregulation, T-cell inactivation, anergy and, often, eventual apoptotic death. In the regulated immune response, mixed populations of anergized and apoptosing T cells can be found. In some cases, anergy appears to lead to death while, in other instances, cells revert to a functional state. This review focuses on recent papers examining each of these topics in an attempt to obtain a preliminary integrated picture of immune regulation in **autoimmune** diseases.

L22 ANSWER 48 OF 92 MEDLINE on STN
95211856. PubMed ID: 7697733. Limited regulatory effect of **T cell receptor**-derived peptides. Hsueh Y P; Yang Y F; Liang H E; Han S H; Lai M Z. (Institute of Microbiology and Immunology, National Yang-Ming University, Taipei, Taiwan, ROC.) Cellular immunology, (1995 Apr 1) 161 (2) 218-25. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.
AB **T cell receptor** (**TCR**)-derived peptides have been used to induce regulatory T cells which recognize T cells of specific elements and downregulate the **autoimmune** response. Consistent with these observations, priming of peptides corresponding to V beta 8 complementarity-determining region 2 (CDR2) was found to specifically suppress the proliferation of V beta 8+ T cells in the draining lymph nodes. Similarly, the generation of V beta 8-dominant T cell responses was prevented locally by vaccination with V beta 8 CDR2 peptides. There was a good correlation between the downregulation of V beta 8+ T cells and the inhibition of the corresponding T cell responses in different lymphoid tissues. No systemic inhibition could be detected even after an interval which would allow the redistribution of the "regulatory T cells." T cells specific for V beta 8 CDR2 peptides was generated following peptide immunization. However, the appearance of these **TCR peptide**-specific T cells was independent of the downregulation of V beta 8+ T cells. The transient and localized inhibitory effects of **TCR**-derived peptides indicate that these peptides have very limited use in regulating specific T cell response.

L22 ANSWER 51 OF 92 MEDLINE on STN
95089157. PubMed ID: 7996672. Regulatory T cell network. Yamamura T. Nippon rinsho. Japanese journal of clinical medicine, (1994 Nov) 52 (11) 2805-10. Ref: 21. Journal code: 0420546. ISSN: 0047-1852. Pub. country: Japan. Language: Japanese.
AB Experimental **autoimmune** encephalomyelitis (EAE) is induced by

myelin specific **autoimmune** T cells that are characterized by a limited **T cell receptor** (**TCR**) heterogeneity. Recent studies demonstrate that regulatory T cells recognizing EAE-associated idiotopes and ergotope are involved in the auto-regulation of EAE. Anti-idiotypic T cells are rapidly induced after T cell vaccination or **TCR peptide** immunization, indicating that the anti-**TCR** response is a recall response and that natural anti-idiotypic network is established in the normal T cell repertoire. Anti-idiotypic T cells are induced not only by vaccination but as the consequence of EAE. In this review, I stress that prevention and treatment of **autoimmune** disease should aim at the re-organization of anti-idiotypic network.

L22 ANSWER 54 OF 92 MEDLINE on STN

94336961. PubMed ID: 8059014. Immunity to **T cell receptor peptides**: theory and applications. Offner H; Hashim G A; Vandenbark A A. (V.A. Medical Center, Portland, OR 97201.) Regulatory peptides, (1994 May 5) 51 (2) 77-90. Ref: 109. Journal code: 8100479. ISSN: 0167-0115. Pub. country: Netherlands. Language: English.

AB In this review, we describe an anti-idiotypic regulatory mechanism that is naturally induced by the **autoimmune** disease process, and that can be boosted by injection of **TCR peptides** that mimic epitopes generated naturally from germline sequences. The striking similarities in the induction and characteristics of rodent and human T cells specific for **TCR peptides** support the generality of the observation, and enhance the probability that this immunoregulatory mechanism will have application in human organ-specific **autoimmune** diseases that are characterized by oligoclonal expression of **TCR** V genes. The major challenges that remain to be resolved to make the **TCR peptide** therapy more widely applicable include (1) establishing disease-relevant V gene biases in individual patients, (2) identifying biologically active **TCR peptide** sequences, and (3) demonstrating that the induction of anti-**TCR peptide** immunity in humans can reduce the pernicious activity of autoreactive T cells putatively directed at organ-specific target antigens.

L22 ANSWER 56 OF 92 MEDLINE on STN

94286565. PubMed ID: 8016104. CDR1 **T-cell receptor** beta-chain peptide induces major histocompatibility complex class II-restricted T-T cell interactions. Broeren C P; Lucassen M A; van Stipdonk M J; van der Zee R; Boog C J; Kusters J G; van Eden W. (Institute of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, University of Utrecht, The Netherlands.) Proceedings of the National Academy of Sciences of the United States of America, (1994 Jun 21) 91 (13) 5997-6001. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB T-T cell interactions have been proposed in postulated network theories of immunoregulation and **autoimmunity**. Despite previous reports of protection induced by **T-cell receptor** (**TcR**)-derived peptides in experimental **autoimmunity**, no evidence for T-T cell interactions by direct recognition of processed TcRs on native T cells was obtained. Here we report that immunization of rats with overlapping sets of peptides of the **TcR** alpha or beta chain allowed us to detect immunogenic **TcR peptides**. Remarkably enough, these **TcR peptides** appeared to cluster within the hypervariable complementarity-determining regions of the **TcR**. Immunization of rats with these **TcR peptides** induced CD4+ **TcR peptide**-specific T cells, which recognized both rDNA **TcR** proteins and the original, arthritogenic T cell in a major histocompatibility complex class II-restricted way. These findings indicate that activated T cells can process and present their own **TcR** in the context of major histocompatibility complex class II molecules and, furthermore, that such peptides can be recognized by **TcR** variable gene-specific T cells.

L22 ANSWER 59 OF 92 MEDLINE on STN

94179834. PubMed ID: 7510746. Immunity to **TCR peptides** in multiple sclerosis. I. Successful immunization of patients with synthetic V beta 5.2 and V beta 6.1 CDR2 peptides. Bourdette D N; Whitham R H; Chou Y K; Morrison W J; Atherton J; Kenny C; Liefeld D; Hashim G A; Offner H;

Vandenbark A A. (Veterans Affairs Medical Center, Portland, OR 97201.)
Journal of immunology (Baltimore, Md. : 1950), (1994 Mar 1) 152 (5) 2510-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Immunization with disease-associated **TCR** V region peptides is an effective treatment for experimental **autoimmune** encephalomyelitis. Myelin basic protein-specific T cells, which induce experimental **autoimmune** encephalomyelitis in many animal strains, may be important in the pathogenesis of multiple sclerosis. Myelin basic protein-specific T cell clones from some multiple sclerosis patients preferentially use **TCR** V genes from the V beta 5.2 and V beta 6.1 families. To assess the safety and immunogenicity of **TCR** V beta 5.2 and V beta 6.1 peptides, we injected 11 multiple sclerosis patients with varying doses of two synthetic peptides, **TCR** V beta 5.2(39-59) and V beta 6.1(39-59), encompassing the CDR2 region of these V gene families. Low doses (100 to 300 micrograms) of peptide induced T cell immunity in 7 of 11 patients to one or both peptides. Delayed type hypersensitivity skin responses to the peptides were observed in three of seven responders, and **TCR peptide**-specific Ab occurred in two of seven T cell responders. Low doses of **TCR peptides** produced no side effects and did not cause broad spectrum immunosuppression. Synthetic **TCR** V region peptides can induce T cell immunity safely in humans and may prove useful in treating human **autoimmune** diseases.

L22 ANSWER 60 OF 92 MEDLINE on STN

94163694. PubMed ID: 8118876. **T cell receptor peptide** therapy for **autoimmune** encephalomyelitis: stronger immunization is necessary for effective vaccination. Matsumoto Y; Tsuchida M; Hanawa H; Abo T. (Department of Immunology, Niigata University School of Medicine, Japan.) Cellular immunology, (1994 Feb) 153 (2) 468-78. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Although **T cell receptor** (**TCR**) **peptide** therapy was initially reported to be a very effective method for prevention of the development of experimental **autoimmune** encephalomyelitis (EAE), it was recently demonstrated that the same peptide immunization led to enhanced and chronic EAE in some cases. In the present study, we examined the effect of the **TCR peptide** (V beta 8.2-39-59) vaccination on the development of EAE by employing several immunization protocols. We found that **TCR peptide** vaccination effectively prevented EAE development only when the peptide was injected with Mycobacterium tuberculosis-enriched CFA in the vicinity of the challenge site. Under such conditions, a sufficient number of peptide-reactive T cells were generated. Flow cytometry and immunohistochemical analyses using anti-peptide antibody and anti-V beta 8.2 mAb revealed that despite the presence of V beta 8.2+ cells, very few peptide-positive T cells appeared in the lymphoid organs throughout the course of EAE. These findings imply that antibodies that are generated after immunization with V beta 8P are hardly accessible to their specific epitopes in the native protein. Insufficient generation of both T cells and antibodies against V beta 8.2-positive T cells may be attributable to the outcome of the therapy. To establish effective **TCR peptide** immunotherapy, these disadvantages should be overcome by using other **TCR** sequences and/or by employing a more suitable adjuvant.

L22 ANSWER 64 OF 92 MEDLINE on STN

93353146. PubMed ID: 7688792. The involvement of **T cell receptor peptide**-specific regulatory CD4+ T cells in recovery from antigen-induced **autoimmune** disease. Kumar V; Sercarz E E. (Department of Microbiology and Molecular Genetics, University of California, Los Angeles 90024.) Journal of experimental medicine, (1993 Sep 1) 178 (3) 909-16. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Experimental allergic encephalomyelitis (EAE) is a prototype for CD4+ T cell-mediated **autoimmune** diseases. Immunization with myelin basic protein (MBP) in B10.PL mice results in EAE, and a majority of animals recover permanently from the disease. Most MBP-reactive encephalitogenic T cells recognize an immunodominant NH2-terminal peptide, Ac1-9, and

predominantly use the **T cell receptor** (TCR) V beta 8.2 gene segment. Here we report that in mice recovering from MBP-induced EAE, peripheral T cells proliferate in response to a single immunodominant **TCR peptide** from the V beta 8.2 chain (amino acids 76-101), indicating natural priming during the course of the disease. Cloned T cells, specific for this **TCR peptide**, specifically downregulate proliferative responses to Ac1-9 in vivo and also protect mice from MBP-induced EAE. These regulatory T cells express CD4 molecules and recognize a dominant peptide from the **TCR** variable framework region of V beta 8.2, in the context of the major histocompatibility complex class II molecule, I-Au, and predominantly use the **TCR** V beta 14 gene segment. This is the first demonstration of the physiological induction of **TCR peptide**-specific CD4+ T cells that result from MBP immunization and that are revealed only during the recovery from disease. The downregulation of disease-causing T cells by **TCR peptide**-specific T cells offers a mechanism for antigen-specific, network-induced recovery from **autoimmune** disease.

L22 ANSWER 70 OF 92 MEDLINE on STN
93213922. PubMed ID: 8461389. Vaccination with **T-cell receptor peptides**. Brostoff S. (Immune Response Corporation, Carlsbad, California.) Immunology series, (1993) 59 203-18. Ref: 42. Journal code: 0404721. ISSN: 0092-6019. Pub. country: United States. Language: English.

L22 ANSWER 79 OF 92 MEDLINE on STN
92273160. PubMed ID: 1591001. The human **T cell receptor** in health and disease. Moss P A; Rosenberg W M; Bell J I. (Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, United Kingdom.) Annual review of immunology, (1992) 10 71-96. Ref: 139. Journal code: 8309206. ISSN: 0732-0582. Pub. country: United States. Language: English.
AB The T cell antigen receptor (**TCR**) recognizes antigen in the form of short peptides bound to a major histocompatibility (MHC) molecule. This review provides a synopsis of the current state of knowledge of the structure and function of the receptor and its possible role in human disease. Analysis of the **T cell receptor** usage of T-cell lines and clones recognizing the same peptide-MHC complex is beginning to shed light onto the structural basis of the **TCR**-**peptide**-MHC complex. Also, it is now apparent that there are two mechanisms by which the **TCR** can interact with the MHC molecule, either through classical peptide interactions or through super-antigens. Finally, we review the role of specific TCRs in human disease. Current evidence in this area is difficult to interpret; however, it is likely that **TCR**-mediated disease susceptibility exists, and its basis at either a germline or somatic level will soon be clarified.

=> d hs
'HS' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

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ABS ---- AB
ALL ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRI ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, CM, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms

HITIND --- IND
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'D' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'
'HIS' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

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The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRI ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, CM, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.
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'E' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'
'GRAZIOSI' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'
'C/AU' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB

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ALL ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRI ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, CM, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and
PY.

To display a particular field or fields,  enter the display field
codes.  For a list of display field codes, enter 'HELP DFIELDS'
at an arrow prompt (=>).  Examples of formats include: 'BIB';
'AB'; 'SO,ST'.  You may specify the format fields in any order,
and the information will be displayed in the same order as the
format specification.

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used with the DISPLAY ACC command to display the record for a
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ENTER DISPLAY FORMAT (BIB):ti

L22  ANSWER 1 OF 92     MEDLINE on STN
TI   Recombinant antibodies with MHC-restricted, peptide-specific, T-cell
     receptor-like specificity: new tools to study antigen presentation and
     TCR-peptide-MHC interactions.


=> e graziosi c/au
E1            1     GRAZIOSI A C/AU
E2            1     GRAZIOSI A M/AU
E3           33 --> GRAZIOSI C/AU
E4            1     GRAZIOSI D/AU
E5           13     GRAZIOSI F/AU
E6           23     GRAZIOSI G/AU
E7            3     GRAZIOSI G C/AU
E8            1     GRAZIOSI LUIGINA/AU
E9            1     GRAZIOSI M E/AU
E10           6     GRAZIOSI P/AU
E11           1     GRAZIOSI P M/AU
E12           5     GRAZIOSI S/AU

=> s e3
L23          33 "GRAZIOSI C"/AU

=> d l23,ti,1-33

L23  ANSWER 1 OF 33     MEDLINE on STN
TI   Immunization with recombinant canarypox vectors expressing
     membrane-anchored glycoprotein 120 followed by glycoprotein 160 boosting
     fails to generate antibodies that neutralize R5 primary isolates of human
     immunodeficiency virus type 1.

L23  ANSWER 2 OF 33     MEDLINE on STN
TI   Immunological and virological responses in HIV-1-infected adults at early
     stage of established infection treated with highly active antiretroviral
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therapy.

L23 ANSWER 3 OF 33 MEDLINE on STN
TI Selective pressure exerted by immunodominant HIV-1-specific cytotoxic T lymphocyte responses during primary infection drives genetic variation restricted to the cognate epitope.

L23 ANSWER 4 OF 33 MEDLINE on STN
TI Analysis of virologic and immunologic events in HIV infection.

L23 ANSWER 5 OF 33 MEDLINE on STN
TI Immunopathogenesis of HIV infection.

L23 ANSWER 6 OF 33 MEDLINE on STN
TI Limited CD4+ T-cell renewal in early HIV-1 infection: effect of highly active antiretroviral therapy.

L23 ANSWER 7 OF 33 MEDLINE on STN
TI Evolutionary pattern of human immunodeficiency virus (HIV) replication and distribution in lymph nodes following primary infection: implications for antiviral therapy.

L23 ANSWER 8 OF 33 MEDLINE on STN
TI Accumulation of human immunodeficiency virus-specific cytotoxic T lymphocytes away from the predominant site of virus replication during primary infection.

L23 ANSWER 9 OF 33 MEDLINE on STN
TI The multi-faceted personality of HIV.

L23 ANSWER 10 OF 33 MEDLINE on STN
TI Evidence for rapid disappearance of initially expanded HIV-specific CD8+ T cell clones during primary HIV infection.

L23 ANSWER 11 OF 33 MEDLINE on STN
TI Virologic and immunologic events in primary HIV infection.

L23 ANSWER 12 OF 33 MEDLINE on STN
TI The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia.

L23 ANSWER 13 OF 33 MEDLINE on STN
TI New concepts in the immunopathogenesis of HIV infection.

L23 ANSWER 14 OF 33 MEDLINE on STN
TI Kinetics of cytokine expression during primary human immunodeficiency virus type 1 infection.

L23 ANSWER 15 OF 33 MEDLINE on STN
TI Antiretroviral monotherapy in early stage human immunodeficiency virus disease has no detectable effect on virus load in peripheral blood and lymph nodes.

L23 ANSWER 16 OF 33 MEDLINE on STN
TI Pathogenic insights from studies of lymphoid tissue from HIV-infected individuals.

L23 ANSWER 17 OF 33 MEDLINE on STN
TI Decreased human immunodeficiency virus type 1 plasma viremia during antiretroviral therapy reflects downregulation of viral replication in lymphoid tissue.

L23 ANSWER 18 OF 33 MEDLINE on STN
TI Comparative analysis of constitutive cytokine expression in peripheral blood and lymph nodes of HIV-infected individuals.

L23 ANSWER 19 OF 33 MEDLINE on STN
TI Effect of anti-V3 antibodies on cell-free and cell-to-cell human immunodeficiency virus transmission.

L23 ANSWER 20 OF 33 MEDLINE on STN
TI Role of lymphoid organs in the pathogenesis of human immunodeficiency virus (HIV) infection.

L23 ANSWER 21 OF 33 MEDLINE on STN
TI Studies in subjects with long-term nonprogressive human immunodeficiency virus infection.

L23 ANSWER 22 OF 33 MEDLINE on STN
TI Intercellular adhesion molecules (ICAM)-1 ICAM-2 and ICAM-3 function as counter-receptors for lymphocyte function-associated molecule 1 in human immunodeficiency virus-mediated syncytia formation.

L23 ANSWER 23 OF 33 MEDLINE on STN
TI Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV.

L23 ANSWER 24 OF 33 MEDLINE on STN
TI Lack of evidence for the dichotomy of TH1 and TH2 predominance in HIV-infected individuals.

L23 ANSWER 25 OF 33 MEDLINE on STN
TI HIV-1 infection in the lymphoid organs.

L23 ANSWER 26 OF 33 MEDLINE on STN
TI The role of lymphoid organs in the immunopathogenesis of HIV infection.

L23 ANSWER 27 OF 33 MEDLINE on STN
TI The role of lymphoid organs in the pathogenesis of HIV infection.

L23 ANSWER 28 OF 33 MEDLINE on STN
TI Kinetics of human immunodeficiency virus type 1 (HIV-1) DNA and RNA synthesis during primary HIV-1 infection.

L23 ANSWER 29 OF 33 MEDLINE on STN
TI HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease.

L23 ANSWER 30 OF 33 MEDLINE on STN
TI New concepts in the immunopathogenesis of human immunodeficiency virus infection.

L23 ANSWER 31 OF 33 MEDLINE on STN
TI Lymphoid organs function as major reservoirs for human immunodeficiency virus.

L23 ANSWER 32 OF 33 MEDLINE on STN
TI Human immunodeficiency virus (HIV) infection in CD4+ T lymphocytes genetically deficient in LFA-1: LFA-1 is required for HIV-mediated cell fusion but not for viral transmission.

L23 ANSWER 33 OF 33 MEDLINE on STN
TI Method for in situ hybridization to polytene chromosomes from ovarian nurse cells of Anopheles gambiae (Diptera: Culicidae).

=> d l23,cbib,ab,1-33

L23 ANSWER 1 OF 33 MEDLINE on STN
2001201554. PubMed ID: 11153085. Immunization with recombinant canarypox vectors expressing membrane-anchored glycoprotein 120 followed by

glycoprotein 160 boosting fails to generate antibodies that neutralize R5 primary isolates of human immunodeficiency virus type 1. Bures R; Gaitan A; Zhu T; **Graziosi C**; McGrath K M; Tartaglia J; Caudrelier P; El Habib R; Klein M; Lazzarin A; Stablein D M; Deers M; Corey L; Greenberg M L; Schwartz D H; Montefiori D C. (Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA.) AIDS research and human retroviruses, (2000 Dec 10) 16 (18) 2019-35. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Antibodies generated by candidate HIV-1 vaccines in a phase I clinical trial were assessed for neutralizing activity with a panel of eight well-characterized, genetically diverse clade B primary isolates having an R5 phenotype. The vaccines consisted of one of three different recombinant canarypox vectors expressing membrane-anchored HIV-1(MN)gp120 (ALVAC vCP205, vCP1433, and vCP1452) followed by boosting with a soluble gp160 hybrid consisting of MNgp120 and the majority of gp41 from strain IIIB. Serum samples from a subset of volunteers in each arm of the trial, containing moderate to high titers of neutralizing antibodies to HIV-1 MN, were analyzed. Competition assays with peptides revealed that the majority of neutralizing activity was specific for the MN-V3 loop. Despite MN-specific neutralization titers that sometimes exceeded 1:500, no neutralization of primary isolates was detected and, in some cases, mild infection enhancement was observed. In addition, little or no neutralization of the HIV-1 IIIB heterologous T cell line-adapted strain of virus was detected. These results reinforce the notion that monovalent HIV-1 ENV is a poor immunogen for generating cross-reactive neutralizing antibodies.

L23 ANSWER 2 OF 33 MEDLINE on STN

2000445616. PubMed ID: 10997391. Immunological and virological responses in HIV-1-infected adults at early stage of established infection treated with highly active antiretroviral therapy. Bart P A; Rizzardi G P; Tambussi G; Chave J P; Chapuis A G; **Graziosi C**; Corpataux J M; Halkic N; Meuwly J Y; Munoz M; Meylan P; Spreen W; McDade H; Yerly S; Perrin L; Lazzarin A; Pantaleo G. (Department of Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland.) AIDS (London, England), (2000 Sep 8) 14 (13) 1887-97. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To evaluate the immunological and virological responses to highly active antiretroviral therapy (HAART) in blood and lymphoid compartments of HIV-1-infected patients at an early stage of infection. DESIGN: An open-label, observational, non-randomized, prospective trial of outpatients attending the Centre of Clinical Investigation in Infectious Diseases, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland. SUBJECTS: Forty-one antiretroviral-naive HIV-1-infected adults with 400 CD4 T cells/microl or greater and 5000 plasma HIV-1-RNA copies/ml or greater were enrolled, and 32 finished the study. Forty-nine HIV-negative individuals were included as controls. All subjects gave written informed consent. INTERVENTIONS: All patients received abacavir 300 mg by mouth every 12 h and amprenavir 1200 mg by mouth every 12 h for 72 weeks. MAIN OUTCOME MEASURES: The extent of immune reconstitution in blood and lymph nodes after 72 weeks of HAART was evaluated, and compared with immunological measures of 49 HIV-negative subjects. RESULTS: Virus replication was effectively suppressed (-3.5 log10 at week 72). Substantial increments of CD4 T cell count in blood and percentage in lymph nodes were observed over time, and these measures were comparable to HIV-negative subjects by week 24 in blood and by week 48 in lymph nodes. The increase was equally distributed between naive and memory CD4 T cells. Recovery of HIV-specific CD4 responses occurred in 40% of patients. CONCLUSION: The initiation of HAART at an early stage of established HIV infection induces systemic quantitative normalization of CD4 T cells, a partial recovery of HIV-specific CD4 cell responses, and effective and durable suppression of virus replication.

L23 ANSWER 3 OF 33 MEDLINE on STN

2000026000. PubMed ID: 10556818. Selective pressure exerted by immunodominant HIV-1-specific cytotoxic T lymphocyte responses during

primary infection drives genetic variation restricted to the cognate epitope. Soudeyns H; Paolucci S; Chappey C; Daucher M B; **Graziosi C**; Vaccarezza M; Cohen O J; Fauci A S; Pantaleo G. (Laboratory of AIDS Immunopathogenesis, Department of Internal Medicine,Centre hospitalier universitaire vaudois, Lausanne, Switzerland.) European journal of immunology, (1999 Nov) 29 (11) 3629-35. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB HIV-specific cytotoxic T lymphocytes (CTL) play a central role in the control of HIV-1 replication during primary infection. It has been hypothesized that the appearance of CTL escape mutants represents an important mechanism by which HIV-1 escapes the host cell-mediated immune response. However, evidences for a direct relationship between CTL responses and emergence of CTL escape mutants are still limited. Here we report detailed longitudinal analysis of DNA sequence variation performed over the entire HIV-1 envelope in two subjects during primary HIV infection. Estimates of the frequencies of synonymous (ds) and non-synonymous (dN) nucleotide substitutions were used to identify regions of the HIV-1 envelope which were subjected to significant levels of selective pressure. These regions were shown to comprise defined epitopes recognized by CTL. Furthermore, dN mutation fixed within these epitopes effectively abolished recognition by the host CTL response. These results provide compelling evidence that the CTL epitope mutations directly resulted from the selective pressure exerted by the virus-specific cytotoxic response.

L23 ANSWER 4 OF 33 MEDLINE on STN

1998359794. PubMed ID: 9693311. Analysis of virologic and immunologic events in HIV infection. **Graziosi C**; Pantaleo G. (Laboratory of AIDS Immunopathogenesis, Department of Internal Medicine, Division of Infectious Diseases, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.) Pathobiology : journal of immunopathology, molecular and cellular biology, (1998) 66 (3-4) 123-7. Journal code: 9007504. ISSN: 1015-2008. Pub. country: Switzerland. Language: English.

AB A number of pathogenic events occurring immediately after the transmission of HIV lead to the establishment of chronic infection. In fact, despite the detection of vigorous virus-specific immune responses during primary infection, HIV is able to establish chronic infection in most of the cases. This is the result of several virologic and immunologic mechanisms that HIV has evolved to escape and/or to weaken virus-specific immune responses. Lymphoid organs represent the primary anatomic site for the establishment of chronic infection, and if highly active antiretroviral therapy is not initiated in early stage disease, there is a progressive destruction of lymphoid tissue that ultimately leads to the profound immunosuppression typical of AIDS. Therefore, analysis of lymphoid organs is crucial for the correct evaluation of the effectiveness of antiretroviral therapy in HIV infection.

L23 ANSWER 5 OF 33 MEDLINE on STN

1998335951. PubMed ID: 9672230. Immunopathogenesis of HIV infection. **Graziosi C**; Soudeyns H; Rizzardi G P; Bart P A; Chapuis A; Pantaleo G. (Department of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) AIDS research and human retroviruses, (1998 Jun) 14 Suppl 2 S135-42. Ref: 76. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L23 ANSWER 6 OF 33 MEDLINE on STN

1998324747. PubMed ID: 9662370. Limited CD4+ T-cell renewal in early HIV-1 infection: effect of highly active antiretroviral therapy. Fleury S; de Boer R J; Rizzardi G P; Wolthers K C; Otto S A; Welbon C C; **Graziosi C**; Knabenhans C; Soudeyns H; Bart P A; Gallant S; Corpataux J M; Gillet M; Meylan P; Schnyder P; Meuwly J Y; Spreen W; Glauser M P; Miedema F; Pantaleo G. (Department of Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland.) Nature medicine, (1998 Jul) 4 (7) 794-801. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB We show that the fraction of proliferating CD4+ lymphocytes is similar in HIV-infected subjects in the early stage of disease and in HIV-negative subjects, whereas the fraction of proliferating CD8+ lymphocytes is increased 6.8-fold in HIV-infected subjects. After initiation of antiviral therapy, there is a late increase in proliferating CD4+ T cells associated with the restoration of CD4+ T-cell counts. These results provide strong support for the idea of limited CD4+ T-cell renewal in the early stage of HIV infection and indicate that after effective suppression of virus replication, the mechanisms of CD4+ T-cell production are still functional in early HIV infection.

L23 ANSWER 7 OF 33 MEDLINE on STN

1998160246. PubMed ID: 9500610. Evolutionary pattern of human immunodeficiency virus (HIV) replication and distribution in lymph nodes following primary infection: implications for antiviral therapy. Pantaleo G; Cohen O J; Schacker T; Vaccarezza M; **Graziosi C**; Rizzardi G P; Kahn J; Fox C H; Schnittman S M; Schwartz D H; Corey L; Fauci A S. (Laboratory of AIDS Immunopathogenesis, Department of Medicine, Centre Hospitalier Vadois, Lausanne, Switzerland.) Nature medicine, (1998 Mar) 4 (3) 341-5. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Evolutionary patterns of virus replication and distribution in lymphoid tissue during the early phases of HIV infection have not been delineated. Lymph node (LN) biopsies were excised from patients at different times after the estimated time of primary infection. Within 3 months of the acute viral syndrome, HIV was mostly present in individual virus-expressing cells in LNs; trapping of virions in the follicular dendritic cell (FDC) network was minimal or absent, but was the predominant form of HIV detected in LNs of subjects with chronic infection, either recent (4-20 months after primary infection) or long-term (>2-3 years after primary infection). Plasma viremia was significantly higher in patients during the first 3 months than in those recently infected; however, there were no significant differences in the number of virus-expressing cells per square millimeter of LN tissue in these two groups. Numbers of virus-expressing cells in lymphoid tissue were significantly lower in the subjects with long-term infection than in the other two groups. Therefore, during the transition from primary to chronic HIV infection, the level of HIV replication in lymphoid tissue remains elevated despite the fact that viremia is significantly downregulated. These findings have implications for therapeutic strategies in primary HIV infection and in recent seroconvertors.

L23 ANSWER 8 OF 33 MEDLINE on STN

1998124449. PubMed ID: 9464802. Accumulation of human immunodeficiency virus-specific cytotoxic T lymphocytes away from the predominant site of virus replication during primary infection. Pantaleo G; Soudeyns H; Demarest J F; Vaccarezza M; **Graziosi C**; Paolucci S; Daucher M B; Cohen O J; Denis F; Biddison W E; Sekaly R P; Fauci A S. (Department of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.. Guiseppe.Pantaleo@chuv.hospvd.ch) . European journal of immunology, (1997 Dec) 27 (12) 3166-73. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Down-regulation of the initial burst of viremia during primary human immunodeficiency virus (HIV) infection is thought to be mediated predominantly by HIV-specific CD8+ cytotoxic T lymphocytes (CTL). This response is associated with major perturbations in the T cell receptor (TCR) repertoire. To investigate the failure of the cellular immune response to adequately control viral spread and replication and to prevent establishment of HIV infection, changes in the TCR repertoire and in the distribution of virus-specific CTL between blood and lymph node were analyzed in three patients with primary infection. By the combined use of clonotype-specific polymerase chain reaction and analysis of the frequency of in vivo activated HIV-specific CTL, it was shown that HIV-specific CTL clones preferentially accumulated in blood as opposed to lymph node. Accumulation of HIV-specific CTL in blood occurred prior to effective down-regulation of virus replication in both blood and lymph node. These

findings should provide new insights into how HIV, and possibly other viruses, elude the immune response of the host during primary infection.

L23 ANSWER 9 OF 33 MEDLINE on STN
1998057302. PubMed ID: 9396595. The multi-faceted personality of HIV. **Graziosi C**; Pantaleo G. Nature medicine, (1997 Dec) 3 (12) 1318-20. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

L23 ANSWER 10 OF 33 MEDLINE on STN
97420772. PubMed ID: 9275214. Evidence for rapid disappearance of initially expanded HIV-specific CD8+ T cell clones during primary HIV infection. Pantaleo G; Soudeyns H; Demarest J F; Vaccarezza M; **Graziosi C**; Paolucci S; Daucher M; Cohen O J; Denis F; Biddison W E; Sekaly R P; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.. Giuseppe.Pantaleo@chuv.hospvd.ch) . Proceedings of the National Academy of Sciences of the United States of America, (1997 Sep 2) 94 (18) 9848-53. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB Down-regulation of the initial burst of viremia during primary HIV infection is thought to be mediated predominantly by HIV-specific cytotoxic T lymphocytes, and the appearance of this response is associated with major perturbations of the T cell receptor repertoire. Changes in the T cell receptor repertoire of virus-specific cytotoxic T lymphocytes were analyzed in patients with primary infection to understand the failure of the cellular immune response to control viral spread and replication. This analysis demonstrated that a significant number of HIV-specific T cell clones involved in the primary immune response rapidly disappeared. The disappearance was not the result of mutations in the virus epitopes recognized by these clones. Evidence is provided that phenomena such as high-dose tolerance or clonal exhaustion might be involved in the disappearance of these monoclonally expanded HIV-specific cytotoxic T cell clones. These findings should provide insights into how HIV, and possibly other viruses, elude the host immune response during primary infection.

L23 ANSWER 11 OF 33 MEDLINE on STN
97245189. PubMed ID: 9089948. Virologic and immunologic events in primary HIV infection. Pantaleo G; **Graziosi C**; Fauci A S. (Laboratory of AIDS Immunopathogenesis, Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.) Springer seminars in immunopathology, (1997) 18 (3) 257-66. Ref: 48. Journal code: 7910384. ISSN: 0344-4325. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

L23 ANSWER 12 OF 33 MEDLINE on STN
97144428. PubMed ID: 8990195. The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia. Pantaleo G; Demarest J F; Schacker T; Vaccarezza M; Cohen O J; Daucher M; **Graziosi C**; Schnittman S S; Quinn T C; Shaw G M; Perrin L; Tambussi G; Lazzarin A; Sekaly R P; Soudeyns H; Corey L; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.. gpantaleo@chuv.hosprol.ch) . Proceedings of the National Academy of Sciences of the United States of America, (1997 Jan 7) 94 (1) 254-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB Following infection of the host with a virus, the delicate balance between virus replication/spread and the immune response to the virus determines the outcome of infection, i.e., persistence versus elimination of the virus. It is unclear, however, what relative roles immunologic and virologic factors play during primary viral infection in determining the subsequent clinical outcome. By studying a cohort of subjects with primary HIV infection, it has been demonstrated that qualitative differences in the primary immune response to HIV, but not quantitative

differences in the initial levels of viremia are associated with different clinical outcomes.

L23 ANSWER 13 OF 33 MEDLINE on STN
96375720. PubMed ID: 8782009. New concepts in the immunopathogenesis of HIV infection. **Graziosi C**; Pantaleo G. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.) Journal of biological regulators and homeostatic agents, (1995 Jul-Sep) 9 (3) 73-5. Ref: 16. Journal code: 8809253. ISSN: 0393-974X. Pub. country: Italy. Language: English.

L23 ANSWER 14 OF 33 MEDLINE on STN
96210653. PubMed ID: 8633076. Kinetics of cytokine expression during primary human immunodeficiency virus type 1 infection. **Graziosi C**; Gantt K R; Vaccarezza M; Demarest J F; Daucher M; Saag M S; Shaw G M; Quinn T C; Cohen O J; Welbon C C; Pantaleo G; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-1876, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1996 Apr 30) 93 (9) 4386-91. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB In the present study, we have determined the kinetics of constitutive expression of a panel of cytokines [interleukin (IL) 2, IL-4, IL-6, IL-10, interferon gamma (IFN-gamma), and tumor necrosis factor alpha (TNF-alpha)] in sequential peripheral blood mononuclear cell samples from nine individuals with primary human immunodeficiency virus infection. Expression of IL-2 and IL-4 was barely detected in peripheral blood mononuclear cells. However, substantial levels of IL-2 expression were found in mononuclear cells isolated from lymph node. Expression of IL-6 was detected in only three of nine patients, and IL-6 expression was observed when transition from the acute to the chronic phase had already occurred. Expression of IL-10 and TNF-alpha was consistently observed in all patients tested, and levels of both cytokines were either stable or progressively increased over time. Similar to IL-10 and TNF-alpha, IFN-gamma expression was detected in all patients; however, in five of nine patients, IFN-gamma expression peaked very early during primary infection. The early peak in IFN-gamma expression coincided with oligoclonal expansions of CD8+ T cells in five of six patients, and CD8+ T cells mostly accounted for the expression of this cytokine. These results indicate that high levels of expression of proinflammatory cytokines are associated with primary infection and that the cytokine response during this phase of infection is strongly influenced by oligoclonal expansions of CD8+ T cells.

L23 ANSWER 15 OF 33 MEDLINE on STN
96183620. PubMed ID: 8603962. Antiretroviral monotherapy in early stage human immunodeficiency virus disease has no detectable effect on virus load in peripheral blood and lymph nodes. Cohen O J; Pantaleo G; Holodniy M; Fox C H; Orenstein J M; Schnittman S; Niu M; **Graziosi C**; Pavlakis G N; Lalezari J; Bartlett J A; Steigbigel R T; Cohn J; Novak R; McMahon D; Bilello J; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892, USA.) Journal of infectious diseases, (1996 Apr) 173 (4) 849-56. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB Initiation of antiretroviral monotherapy early in the course of infection with human immunodeficiency virus may result in a temporary slowing in the rate of disease progression; however, little is known about the virologic effects of early therapy. Virus load was measured in peripheral blood and lymph nodes from 16 antiretroviral-naive patients with a mean CD4 T lymphocyte count of 659 cells/microliter at baseline and after 8 weeks of either no treatment or zidovudine therapy. CD4 T lymphocyte counts and all virologic parameters examined remained unchanged regardless of zidovudine treatment status. Histopathology and virus distribution within lymph nodes remained constant between baseline and week 8 in each patient, indicating that the virologic and histologic parameters examined in a single lymph node are representative of a systemic process. Early

antiretroviral monotherapy with zidovudine had no effect on virologic parameters in this group of patients with relatively high CD4 T lymphocyte counts and low measures of virus load at baseline.

L23 ANSWER 16 OF 33 MEDLINE on STN

96173458. PubMed ID: 8595512. Pathogenic insights from studies of lymphoid tissue from HIV-infected individuals. Cohen O J; Pantaleo G; Schwartzentruber D J; **Graziosi C**; Vaccarezza M; Fauci A S. (National Institute of Allergy and Infectious Diseases, Laboratory of Immunoregulation, National Institutes of Health, Bethesda, MD 20892, USA.) Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association, (1995) 10 Suppl 1 S6-14. Ref: 59. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB Studies of lymphoid tissue from HIV-infected individuals have provided critical insights into the pathogenesis of HIV disease. Systemic dissemination of virus via the lymphatic system occurs at a very early stage after infection. Explosive viral replication within lymphoid tissue ensues, before the development of cell-mediated and humoral immune responses. By the time potent immune responses downregulate viral expression, an immense viral reservoir within lymphoid tissue has already been established. During the stage of dichotomy in viral load between lymph node and peripheral blood, the viral reservoir is maintained by the ability of the follicular dendritic cells (FDC) network to efficiently trap extracellular virions, as well as by immunologic and microenvironmental factors favoring infection of susceptible cells and sequestration of cells already infected. Degeneration of the FDC network and wholesale disruption of lymphoid architecture herald late-stage disease. The dysfunctional lymphoid tissue contributes directly to immunodeficiency and to sharp increases in viral burden and replication as mechanical and immune controls are lost. Studies in HIV-infected long-term nonprogressors indicate that these individuals are able to maintain cell-mediated and humoral immune responses against HIV. These immune responses are responsible, at least in part, for the maintenance of intact lymphoid tissue architecture and the low levels of viral burden and replication detected in these individuals. Studies of the effect of antiretroviral therapy on HIV infection in lymphoid tissue show that decreases in plasma viremia are associated with and most likely are caused by decreases in viral replication within lymphoid tissue. Further understanding of the pathogenic mechanisms within lymphoid tissue will have important implications for early intervention aimed at inducing a long-term nonprogressor state (i.e., preventing disruption of lymphoid tissue integrity), and later intervention aimed at arresting or even reversing damage to the lymphoid system.

L23 ANSWER 17 OF 33 MEDLINE on STN

95320206. PubMed ID: 7597072. Decreased human immunodeficiency virus type 1 plasma viremia during antiretroviral therapy reflects downregulation of viral replication in lymphoid tissue. Cohen O J; Pantaleo G; Holodniy M; Schnittman S; Niu M; **Graziosi C**; Pavlakis G N; Lalezari J; Bartlett J A; Steigbigel R T; +. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1995 Jun 20) 92 (13) 6017-21. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Although several immunologic and virologic markers measured in peripheral blood are useful for predicting accelerated progression of human immunodeficiency virus (HIV) disease, their validity for evaluating the response to antiretroviral therapy and their ability to accurately reflect changes in lymphoid organs remain unclear. In the present study, changes in certain virologic markers have been analyzed in peripheral blood and lymphoid tissue during antiretroviral therapy. Sixteen HIV-infected individuals who were receiving antiretroviral therapy with zidovudine for > or = 6 months were randomly assigned either to continue on zidovudine alone or to add didanosine for 8 weeks. Lymph node biopsies were performed at baseline and after 8 weeks. Viral burden (i.e., HIV DNA

copies per 10^6 mononuclear cells) and virus replication in mononuclear cells isolated from peripheral blood and lymph node and plasma viremia were determined by semiquantitative polymerase chain reaction assays. Virologic and immunologic markers remained unchanged in peripheral blood and lymph node of patients who continued on zidovudine alone. In contrast, a decrease in virus replication in lymph nodes was observed in four of six patients who added didanosine to their regimen, and this was associated with a decrease in plasma viremia. These results indicate that decreases in plasma viremia detected during antiretroviral therapy reflect downregulation of virus replication in lymphoid tissue.

L23 ANSWER 18 OF 33 MEDLINE on STN

95273781. PubMed ID: 7754207. Comparative analysis of constitutive cytokine expression in peripheral blood and lymph nodes of HIV-infected individuals. **Graziosi C;** Pantaleo G; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.) Research in immunology, (1994 Oct-Dec) 145 (8-9) 602-5; discussion 605-7. Ref: 15. Journal code: 8907467. ISSN: 0923-2494. Pub. country: France. Language: English.

L23 ANSWER 19 OF 33 MEDLINE on STN

95145531. PubMed ID: 7843235. Effect of anti-V3 antibodies on cell-free and cell-to-cell human immunodeficiency virus transmission. Pantaleo G; Demarest J F; Vaccarezza M; **Graziosi C;** Bansal G P; Koenig S; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) European journal of immunology, (1995 Jan) 25 (1) 226-31. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The present study was undertaken to compare the effects of a type-specific (HIV-1 MN) anti-V3 antibody on in vitro human immunodeficiency virus (HIV) infection of peripheral blood mononuclear cells in systems of cell-free versus cell-to-cell transmission of virus. Anti-V3 antibody completely prevented HIV-1 infection when cell-free virus was the sole mechanism of infection. A significant reduction of the neutralizing activity of the anti-V3 antibody was observed when infectivity was dependent on both cell-free and cell-to-cell mechanisms of infection. Furthermore, when cell-to-cell transfer of virions was the primary mechanism of HIV-1 infection, inhibition of HIV-1 infection was not observed. Therefore, a potent neutralizing antibody with a single epitope specificity failed to effectively control dissemination of a persistent HIV-1 infection in a system characterized predominantly by cell-to-cell transfer of virus.

L23 ANSWER 20 OF 33 MEDLINE on STN

95122080. PubMed ID: 7821924. Role of lymphoid organs in the pathogenesis of human immunodeficiency virus (HIV) infection. Pantaleo G; **Graziosi C;** Demarest J F; Cohen O J; Vaccarezza M; Gantt K; Muro-Cacho C; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) Immunological reviews, (1994 Aug) 140 105-30. Ref: 79. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB The pathogenic mechanisms of HIV disease are multifactorial and multi-phasic. The common denominator of the disease is the profound immunosuppression that occurs in the vast majority of infected patients. Studies in lymphoid tissues in HIV disease have provided considerable insight into the pathogenic processes involved from the earliest phases of infection through the advanced stages. Following primary infection, virus is disseminated throughout the body and seeds the lymphoid tissue where its replication is only incompletely suppressed and where a reservoir of virus is established. Extracellular virus is trapped within the FDC of the lymph node germinal centers and serves as a source of infection for cells which reside in or migrate through the lymph node throughout the course of infection even during the early and often prolonged asymptomatic period. Eventually, the architecture of the lymphoid tissue is destroyed, compounding the immune dysfunction that results from the depletion of CD4+

T cells. In this regard, the lymphoid tissue of LTNPs is relatively intact and viral burden and replication is considerably lower in the peripheral blood and lymph node mono-nuclear cells of LTNPs than in individuals whose disease progresses. Cytokines probably play a major role in the modulation of HIV expression in the milieu of the lymphoid tissue. Further understanding of the pathogenic mechanisms operative in the lymphoid tissues of HIV-infected individuals will have important implications in the design of therapeutic strategies involving both antiretroviral and immunomodulatory approaches.

L23 ANSWER 21 OF 33 MEDLINE on STN

95107359. PubMed ID: 7808486. Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. Pantaleo G; Menzo S; Vaccarezza M; **Graziosi C**; Cohen O J; Demarest J F; Montefiori D; Orenstein J M; Fox C; Schrager L K; +. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md 20892-1876.) New England journal of medicine, (1995 Jan 26) 332 (4) 209-16. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

AB BACKGROUND. In a small percentage of persons infected with human immunodeficiency virus type 1 (HIV-1), there is no progression of disease and CD4+ T-cell counts remain stable for many years. Studies of the histopathological, virologic, and immunologic characteristics of these persons may provide insight into the pathogenic mechanisms that lead to HIV disease and the protective mechanisms that prevent progression to overt disease. METHODS AND RESULTS. We studied 15 subjects with long-term nonprogressive HIV infection and 18 subjects with progressive HIV disease. Nonprogressive infection was defined as seven or more years of documented HIV infection, with more than 600 CD4+ T cells per cubic millimeter, no antiretroviral therapy, and no HIV-related disease. Lymph nodes from the subjects with nonprogressive infection had significantly fewer of the hyperplastic features, and none of the involuted features, characteristic of nodes from subjects with progressive disease. Plasma levels of HIV-1 RNA and the viral burden in peripheral-blood mononuclear cells were both significantly lower in the subjects with nonprogressive infection than in those with progressive disease ($P = 0.003$ and $P = 0.015$, respectively). HIV could not be isolated from the plasma of the former, who also had significantly higher titers of neutralizing antibodies than the latter. There was viral replication, however, in the subjects with nonprogressive infection, and virus was consistently cultured from mononuclear cells from the lymph nodes. In the lymph nodes virus "trapping" varied with the degree of formation of germinal centers, and few cells expressing virus were found by in situ hybridization. HIV-specific cytotoxic activity was detected in all seven subjects with nonprogressive infection who were tested. CONCLUSIONS. In persons who remain free of disease for many years despite HIV infection the viral load is low, but viral replication persists. Lymph-node architecture and immune function appear to remain intact.

L23 ANSWER 22 OF 33 MEDLINE on STN

94374430. PubMed ID: 7916296. Intercellular adhesion molecules (ICAM)-1 ICAM-2 and ICAM-3 function as counter-receptors for lymphocyte function-associated molecule 1 in human immunodeficiency virus-mediated syncytia formation. Butini L; De Fougerolles A R; Vaccarezza M; **Graziosi C**; Cohen D I; Montroni M; Springer T A; Pantaleo G; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) European journal of immunology, (1994 Sep) 24 (9) 2191-5. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB It has been previously demonstrated that lymphocyte function-associated molecule 1 (LFA-1) plays a major role in human immunodeficiency virus (HIV)-mediated syncytia formation. In the present study we investigated the involvement of intercellular adhesion molecule-1 (ICAM-1), ICAM-2 and ICAM-3 in the process. The ability of monoclonal antibodies (mAb) directed against ICAM-1, ICAM-2 and ICAM-3 to block syncytia was analyzed

either in phytohemagglutinin (PHA) activated lymphocytes infected in vitro with primary or laboratory strains of HIV or by coculturing a T cell line stably expressing HIV envelope with PHA-activated lymphocytes. Complete inhibition of syncytia formation was observed only by the simultaneous addition to the cell cultures of all (i.e. anti-ICAM-1, anti-ICAM-2 and anti-ICAM-3) mAb. These results indicate that the interaction between LFA-1 and ICAM is a critical step in HIV-mediated syncytia formation, and that ICAM-1, ICAM-2 and ICAM-3 are the receptor molecules for the LFA-1-dependent syncytia formation.

L23 ANSWER 23 OF 33 MEDLINE on STN

94322938. PubMed ID: 8047166. Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV. Pantaleo G; Demarest J F; Soudeyns H; **Graziosi C**; Denis F; Adelsberger J W; Borrow P; Saag M S; Shaw G M; Sekaly R P; +. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.) Nature, (1994 Aug 11) 370 (6489) 463-7. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A SIGNIFICANT proportion (up to 70%) of individuals experience an acute clinical syndrome of varying severity associated with primary infection with the human immunodeficiency virus (HIV). We report here studies on six individuals who showed an acute HIV syndrome which generally resolved within four weeks, concomitant with a dramatic downregulation of viraemia. To characterize the T-cell-mediated primary immune response to HIV, we used combined semiquantitative polymerase chain reaction assay and cytofluorometry to analyse the T-cell antigen receptor repertoire in sequential peripheral blood mononuclear cells from the patients. We found major oligoclonal expansions in a restricted set of variable-domain beta-chain (V beta) families. Cells expressing the expanded V beta s predominantly expressed the CD8 T-cell differentiation antigen and mediated HIV-specific cytotoxicity. Major oligoclonal expansions of these CD8+ T lymphocytes may represent an important component of the primary immune response to viral infections and may help to clarify both the immunopathogenic and the protective mechanisms of HIV infection.

L23 ANSWER 24 OF 33 MEDLINE on STN

94294789. PubMed ID: 8023143. Lack of evidence for the dichotomy of TH1 and TH2 predominance in HIV-infected individuals. **Graziosi C**; Pantaleo G; Gantt K R; Fortin J P; Demarest J F; Cohen O J; Sekaly R P; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) Science, (1994 Jul 8) 265 (5169) 248-52. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB A switch from a T helper 1 (TH1) cytokine phenotype to a TH2 phenotype has been proposed as a critical element in the progression of human immunodeficiency virus (HIV) disease. Here, constitutive cytokine expression was analyzed in unfractionated and sorted cell populations isolated from peripheral blood and lymph nodes of HIV-infected individuals at different stages of disease. Expression of interleukin-2 (IL-2) and IL-4 was barely detectable (or undetectable) regardless of the stage of disease. CD8+ cells expressed large amounts of interferon gamma and IL-10, and the levels of these cytokines remained stably high throughout the course of infection. Furthermore, similar patterns of cytokine expression were observed after stimulation in vitro of purified CD4+ T cell populations obtained from HIV-infected individuals at different stages of disease. These results indicate that a switch from the TH1 to the TH2 cytokine phenotype does not occur during the progression of HIV disease.

L23 ANSWER 25 OF 33 MEDLINE on STN

94213727. PubMed ID: 8161447. HIV-1 infection in the lymphoid organs. **Graziosi C**; Pantaleo G; Demarest J F; Cohen O J; Vaccarezza M; Butini L; Montroni M; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.) AIDS (London, England), (1993 Nov) 7 Suppl 2

Suppl 1 S19-23. Ref: 29. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB AIM: To develop a model of HIV disease progression. METHOD: Comparative analysis of viral burden and replication between peripheral blood and lymphoid organs and of the changes in viral distribution in the lymphoid tissue. RESULTS: In early-stage disease HIV-1-infected cells were sequestered in the lymphoid tissue, and the viral particles were concentrated and trapped in the germinal centers. The dichotomy in viral burden and viral replication between peripheral blood and lymphoid tissue was related to the histopathologic abnormalities associated with different stages of disease. CONCLUSIONS: These histopathologic abnormalities may not only explain the changes in viral distribution observed in the lymphoid tissue in different stages of the disease, but may also reflect different functional states of the immune system during the progression of HIV-1 infection from early- to late-stage disease.

L23 ANSWER 26 OF 33 MEDLINE on STN

93371743. PubMed ID: 8363784. The role of lymphoid organs in the immunopathogenesis of HIV infection. Pantaleo G; **Graziosi C**; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.) AIDS (London, England), (1993) 7 Suppl 1 S19-23. Ref: 29. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

L23 ANSWER 27 OF 33 MEDLINE on STN

93350202. PubMed ID: 8102261. The role of lymphoid organs in the pathogenesis of HIV infection. Pantaleo G; **Graziosi C**; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) Seminars in immunology, (1993 Jun) 5 (3) 157-63. Ref: 42. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB Following primary human immunodeficiency virus (HIV) infection, HIV disease is characterized by a prolonged period, usually lasting several years, of clinical latency. During this period viremia is generally very low or undetectable, the number of infected cells (i.e. viral burden) in the blood are very low, and the levels of viral replication in these cells are barely detectable. These findings have been interpreted as a reflection of a phase of inactive HIV disease during which time HIV replicates very slowly or its replicating ability is kept under control by effective HIV specific immune responses. However, during this period a general deterioration of immune function and progressive depletion of CD4+ T cells occur; the inevitable outcome is clinically apparent disease. In the present article, we describe a model of disease development in which HIV infection is both active and progressive in the lymphoid organs during the clinically latent period of HIV infection when there are few, if any, signs of disease activity in peripheral blood.

L23 ANSWER 28 OF 33 MEDLINE on STN

93342000. PubMed ID: 8341646. Kinetics of human immunodeficiency virus type 1 (HIV-1) DNA and RNA synthesis during primary HIV-1 infection. **Graziosi C**; Pantaleo G; Butini L; Demarest J F; Saag M S; Shaw G M; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) Proceedings of the National Academy of Sciences of the United States of America, (1993 Jul 15) 90 (14) 6405-9. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB HIV-1 replication and viral burden in peripheral blood mononuclear cells (PBMC) have been reported to be high in primary infection but generally very low during the prolonged period of clinical latency. It is uncertain precisely when this transition occurs during the HIV-1 infection and what the relationship is between the changes in HIV-1 replication versus the clearance of infected cells in the overall control of viral replication. In the present study, the kinetics of viral burden (i.e., frequency of HIV-1-infected cells) and replication during primary and early-chronic infection were analyzed in PBMC of four acutely infected individuals.

high frequencies of HIV-1 infected cells and high levels of virus replication were observed in PBMC after primary HIV-1 infection. Down-regulation of virus replication in PBMC was observed in all four patients coincident with the emergence of HIV-1-specific immune responses. Other parameters of virus replication, such as circulating plasma p24 antigen and plasma viremia showed similar kinetics. In contrast, a significant decline in viral burden in PBMC was observed in only one of four patients. These results indicate that the down-regulation in the levels of virus replication associated with the clinical transition from acute to chronic infection does not necessarily reflect a reduction in viral burden, thus suggesting the involvement of additional factors. Identification of these factors will be important in elucidating the host mechanisms involved in the early control of HIV-1 infection and disease.

L23 ANSWER 29 OF 33 MEDLINE on STN

93205123. PubMed ID: 8455722. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Pantaleo G; **Graziosi C**; Demarest J F; Butini L; Montroni M; Fox C H; Orenstein J M; Kotler D P; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.) Nature, (1993 Mar 25) 362 (6418) 355-8. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Primary infection with the human immunodeficiency virus (HIV) is generally followed by a burst of viraemia with or without clinical symptoms. This in turn is followed by a prolonged period of clinical latency. During this period there is little, if any, detectable viraemia, the numbers of infected cells in the blood are very low, and it is extremely difficult to demonstrate virus expression in these cells. We have analysed viral burden and levels of virus replication simultaneously in the blood and lymphoid organs of the same individuals at various stages of HIV disease. Here we report that in early-stage disease there is a dichotomy between the levels of viral burden and virus replication in peripheral blood versus lymphoid organs. HIV disease is active in the lymphoid tissue throughout the period of clinical latency, even at times when minimal viral activity is demonstrated in blood.

L23 ANSWER 30 OF 33 MEDLINE on STN

93125629. PubMed ID: 8093551. New concepts in the immunopathogenesis of human immunodeficiency virus infection. Pantaleo G; **Graziosi C**; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) New England journal of medicine, (1993 Feb 4) 328 (5) 327-35. Ref: 107. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

L23 ANSWER 31 OF 33 MEDLINE on STN

92052186. PubMed ID: 1682922. Lymphoid organs function as major reservoirs for human immunodeficiency virus. Pantaleo G; **Graziosi C**; Butini L; Pizzo P A; Schnittman S M; Kotler D P; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) Proceedings of the National Academy of Sciences of the United States of America, (1991 Nov 1) 88 (21) 9838-42. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The total number of human immunodeficiency virus type 1 (HIV-1)-infected circulating CD4+ T lymphocytes is considered to be a reflection of the HIV burden at any given time during the course of HIV infection. However, the low frequency of HIV-infected circulating CD4+ T lymphocytes and the low level or absence of plasma viremia in the early stages of infection do not correlate with the progressive immune dysfunction characteristic of HIV infection. In this study, we have determined whether HIV-infected circulating CD4+ T lymphocytes are a correct reflection of the total pool of HIV-infected CD4+ T cells (i.e., HIV burden). To this end, HIV burden has been comparatively analyzed in peripheral blood and lymphoid tissues (lymph nodes, adenoids, and tonsils) from the same patients. The presence

of HIV-1 DNA in mononuclear cells isolated simultaneously from peripheral blood and lymphoid tissues of the same patients was determined by polymerase chain reaction amplification. We found that the frequency of HIV-1-infected cells in unfractionated or sorted CD4+ cell populations isolated from lymphoid tissues was significantly higher (0.5-1 log10 unit) than the frequency in peripheral blood. Comparable results were obtained in five HIV seropositive patients in the early stages of disease and in one patient with AIDS. These results demonstrate that a heavy viral load does reside in the lymphoid organs, indicating that they may function as major reservoirs for HIV. In addition, the finding of a heavy viral load in the lymphoid organs of patients in the early stages of disease may explain the progressive depletion of CD4+ T lymphocytes and the immune dysfunction associated with the early stages of HIV infection.

L23 ANSWER 32 OF 33 MEDLINE on STN

91108353. PubMed ID: 1671082. Human immunodeficiency virus (HIV) infection in CD4+ T lymphocytes genetically deficient in LFA-1: LFA-1 is required for HIV-mediated cell fusion but not for viral transmission. Pantaleo G; Butini L; **Graziosi C**; Poli G; Schnittman S M; Greenhouse J J; Gallin J I; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.) Journal of experimental medicine, (1991 Feb 1) 173 (2) 511-4. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB In the present study, we demonstrated that expression of the LFA-1 molecule is necessary for cell fusion and syncytia formation in human immunodeficiency virus (HIV)-infected CD4+ T lymphocytes. In contrast, the lack of expression of LFA-1 does not influence significantly cell-to-cell transmission of HIV. In fact, LFA-1- T lymphocytes obtained from a leukocyte adhesion deficiency patient were unable to fuse and form syncytia when infected with HIV-1 or HIV-2, despite the fact that efficiency of HIV infection (i.e., virus entry, HIV spreading, and levels of virus replication) was comparable with that observed in LFA-1+ T lymphocytes. In addition, we provide evidence that LFA-1 by mediating cell fusion contributes to the depletion of HIV-infected CD4+ T lymphocytes in vitro.

L23 ANSWER 33 OF 33 MEDLINE on STN

91039185. PubMed ID: 2231626. Method for in situ hybridization to polytene chromosomes from ovarian nurse cells of Anopheles gambiae (Diptera: Culicidae). **Graziosi C**; Sakai R K; Romans P; Miller L H; Wellems T E. (Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.) Journal of medical entomology, (1990 Sep) 27 (5) 905-12. Journal code: 0375400. ISSN: 0022-2585. Pub. country: United States. Language: English.

AB A procedure for in situ hybridization to polytene chromosomes from the ovarian nurse cells of Anopheles gambiae Giles has been developed. This procedure involves a modification of established methods for Drosophila larval salivary gland polytene chromosomes. Treatment of chromosome squashes with xylene followed by slow rehydration provides required resolution of chromosome banding patterns, possibly because fatty contaminants are removed from ovarian nurse cell preparations. Using this procedure, unique DNA sequences from a genomic library of An. gambiae have been mapped on adult mosquito polytene chromosomes. The ability to locate genetic markers on chromosomes will allow correlation of physical and genetic maps. Such maps will facilitate identification of genetic loci and expand our knowledge of the genomic organization of An. gambiae.

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E1          34      ROMAGNANI P/AU
E2           6      ROMAGNANI PAOLA/AU
E3         301 --> ROMAGNANI S/AU
E4          12      ROMAGNANI SERGIO/AU
E5           8      ROMAGNANO A/AU
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E6            6      ROMAGNANO L/AU
E7            2      ROMAGNANO L C/AU
E8            1      ROMAGNANO LINDA/AU
E9           12      ROMAGNANO M A/AU
E10           1      ROMAGNANO S/AU
E11          30      ROMAGNE F/AU
E12           1      ROMAGNE O/AU

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L24          12 "ROMAGNANI SERGIO"/AU

=> d l24,ti,1-12

L24  ANSWER 1 OF 12     MEDLINE on STN
TI   New therapeutic strategies in allergic diseases.

L24  ANSWER 2 OF 12     MEDLINE on STN
TI   Human CD8+CD25+ thymocytes share phenotypic and functional features with
     CD4+CD25+ regulatory thymocytes.

L24  ANSWER 3 OF 12     MEDLINE on STN
TI   Selective deficiency of naive CD4+ T-lymphocytes in a child with
     congenital lymphoedema.

L24  ANSWER 4 OF 12     MEDLINE on STN
TI   An alternatively spliced variant of CXCR3 mediates the inhibition of
     endothelial cell growth induced by IP-10, Mig, and I-TAC, and acts as
     functional receptor for platelet factor 4.

L24  ANSWER 5 OF 12     MEDLINE on STN
TI   T helper type 1 lymphocytes drive inflammation in human atherosclerotic
     lesions.

L24  ANSWER 6 OF 12     MEDLINE on STN
TI   The novel synthetic immune response modifier R-848 (Resiquimod) shifts
     human allergen-specific CD4+ TH2 lymphocytes into IFN-gamma-producing
     cells.

L24  ANSWER 7 OF 12     MEDLINE on STN
TI   Phenotype, localization, and mechanism of suppression of CD4(+)CD25(+)
     human thymocytes.

L24  ANSWER 8 OF 12     MEDLINE on STN
TI   ["Sarcoidosis-like" granulomatous disease in patients with common variable
     hypogammaglobulinemia].
     Malattia granulomatosa "sarcoidosi-simile" in pazienti con
     ipogammaglobulinemia comune variabile.

L24  ANSWER 9 OF 12     MEDLINE on STN
TI   Type 1 T helper cells specific for Candida albicans antigens in peripheral
     blood and vaginal mucosa of women with recurrent vaginal candidiasis.

L24  ANSWER 10 OF 12     MEDLINE on STN
TI   Role of low nuclear grading of renal carcinoma cells in the functional
     profile of tumor-infiltrating T cells.

L24  ANSWER 11 OF 12     MEDLINE on STN
TI   Th2-oriented profile of male offspring T cells present in women with
     systemic sclerosis and reactive with maternal major histocompatibility
     complex antigens.

L24  ANSWER 12 OF 12     MEDLINE on STN
TI   Lymphocytes.


=> d his
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     (FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

     FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
                E MARCHALONIS JOHN J/IN
L1             2 S E3

     FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
                E MARCHALONIS J J/IN
L2             5 S E2 OR E3

     FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
                E MARCHALONIS J J/AU
L3           256 S E2-E5
L4            75 S L3 AND (TCR OR T-CELL RECEPTOR)
L5             4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6             0 S L4 AND (TH1 (W) TH2)

     FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7          9668 S (TCR OR T-CELL RECEPTOR)
L8          7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9           816 S L8 AND (V BETA)
L10          123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11           39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12           38 S L11 NOT L1

     FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004
L13        24107 S (T CELL RECEPTOR OR TCR)
L14         1326 S L13 AND (TH1 OR TH2 OR T-HELPER 1 OR T-HELPER 2)
L15           18 S L14 AND (ALTERED PEPTIDE LIGANDS)
                E EVAVOLD B D/AU
L16           33 S E2-E4
                E MADRENAS J/AU
L17           65 S E3 OR E4
L18           28 S L17 AND (TCR OR T-CELL RECEPTOR)
L19          229 S L14 AND (AUTOIMMUN? OR IMMUNE DYSFUNCTION OR CYTOKINE DYSFUNC
L20           65 S L19 AND (VACCIN? OR IMMUNIZ?)
L21          234 S L13 AND (TCR PEPTIDE? OR T-CELL RECEPTOR PEPTIDE? OR T-CELL R
L22           92 S L21 AND AUTOIMMUN?
                E GRAZIOSI C/AU
L23           33 S E3
                E ROMAGNANI S/AU
L24           12 S E4

=> e romagnani s/au
E1            34      ROMAGNANI P/AU
E2             6      ROMAGNANI PAOLA/AU
E3           301 --> ROMAGNANI S/AU
E4            12      ROMAGNANI SERGIO/AU
E5             8      ROMAGNANO A/AU
E6             6      ROMAGNANO L/AU
E7             2      ROMAGNANO L C/AU
E8             1      ROMAGNANO LINDA/AU
E9            12      ROMAGNANO M A/AU
E10            1      ROMAGNANO S/AU
E11           30      ROMAGNE F/AU
E12            1      ROMAGNE O/AU

=> s e3
L25          301 "ROMAGNANI S"/AU

=> s l25 and switch
         16436 SWITCH
L26          6 L25 AND SWITCH

=> d l26,ti,1-6
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L26 ANSWER 1 OF 6 MEDLINE on STN
TI Th1 and th2 responses, HIV-1 coreceptors, and HIV-1 infection.

L26 ANSWER 2 OF 6 MEDLINE on STN
TI Role of hormone-controlled T-cell cytokines in the maintenance of pregnancy.

L26 ANSWER 3 OF 6 MEDLINE on STN
TI Phosphorothioate oligodeoxynucleotides promote the in vitro development of human allergen-specific CD4+ T cells into Th1 effectors.

L26 ANSWER 4 OF 6 MEDLINE on STN
TI Role of TH1/TH2 cytokines in HIV infection.

L26 ANSWER 5 OF 6 MEDLINE on STN
TI Th1 versus Th2 responses in AIDS.

L26 ANSWER 6 OF 6 MEDLINE on STN
TI An alternative view of the Th1/Th2 **switch** hypothesis in HIV infection.

=> d 126,cbib,ab,1,4-6

L26 ANSWER 1 OF 6 MEDLINE on STN
2001636967. PubMed ID: 11693442. Th1 and th2 responses, HIV-1 coreceptors, and HIV-1 infection. Galli G; Annunziato F; Cosmi L; Manetti R; Maggi E; **Romagnani S**. (Department of Internal Medicine, University of Florence, Italy.) Journal of biological regulators and homeostatic agents, (2001 Jul-Sep) 15 (3) 308-13. Ref: 43. Journal code: 8809253. ISSN: 0393-974X. Pub. country: Italy. Language: English.
AB The Th1/Th2 model provides an interesting paradigm for understanding several pathophysiological processes and possibly for developing new immunotherapeutical strategies. In HIV-1 infection the interaction between the type of HIV-1 strain and the pathway of the ongoing T-cell effector response, despite its complexity, may represent one of the crucial mechanisms in determining the outcome of virus infection. While the possibility of an HIV-1-driven Th1 to Th2 **switch** of the immune response is still debated, evidence is accumulating to suggest that cytokines produced during an immune response can contribute to promote a selective pressure toward the evolution of HIV-1 viral strains with different tropism. This article summarizes the results of our recent studies in which the expression of CCR5 and CXCR4 HIV-1 co-receptors, as well as the activity of R5- or X4- tropic strains of HIV-1 in different in vitro models of Th1/Th2 polarization was analyzed.

L26 ANSWER 4 OF 6 MEDLINE on STN
95122085. PubMed ID: 7821929. Role of TH1/TH2 cytokines in HIV infection. **Romagnani S**; Del Prete G; Manetti R; Ravina A; Annunziato F; De Carli M; Mazzetti M; Piccinni M P; D'Elios M M; Parronchi P; +. (Department of Allergy & Clinical Immunology, University of Florence, Italy.) Immunological reviews, (1994 Aug) 140 73-92. Ref: 65. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.
AB Different experimental approaches were used to prove or disprove the "TH1/TH2 **switch** theory" of HIV-infection. No increase, or even a decrease, in the production of TH2-type cytokines (IL-4, IL-5, and IL-10) by either bulk circulating mononuclear cells or CD4+ T-cell clones generated by PHA stimulation of single T cells from HIV-infected individuals in all stages of disease compared to HIV-negative donors was observed. However, enhanced proportions of CD4+ T-cell clones able to produce both TH1-type and TH2-type cytokines (TH0 clones) were derived from either skin-infiltrating, in vivo-activated, T cells or in vitro antigen-stimulated peripheral blood T cells of HIV-infected individuals. Of note, TH1, TH2 and TH0 clones obtained from HIV-seronegative healthy donors showed different ability to support viral replication after infection with HIV in vitro. All TH2 and most TH0 clones supported HIV

replication efficiently, whereas TH1 clones did not. These results suggest preferential HIV replication in T cells producing TH2-type cytokines rather than TH1/TH2 **switch** in HIV infection.

L26 ANSWER 5 OF 6 MEDLINE on STN
95032865. PubMed ID: 7946051. Th1 versus Th2 responses in AIDS. **Romagnani S**; Maggi E. (Istituto di Clinica Medica 3, University of Florence, Italy.) Current opinion in immunology, (1994 Aug) 6 (4) 616-22. Ref: 35. Journal code: 8900118. ISSN: 0952-7915. Pub. country: ENGLAND: United Kingdom. Language: English.
AB During the past two years, a simple theory that seeks to explain what causes the progression of HIV-infected individuals to AIDS has been gaining support. The theory holds that HIV-infected people **switch** from a T-helper type 1 (Th1) to a T-helper type 2 (Th2) state as the disease progresses. However the experimental data do not support the concept that a Th1/Th2 **switch** occurs in the majority of HIV-infected subjects, although it is conceivable that HIV-infected individuals who mount sustained and chronic Th2-type responses, as a result of allergic disorders and helminthic infestations, may undergo more active HIV replication and therefore progress faster to full-blown disease.

L26 ANSWER 6 OF 6 MEDLINE on STN
95000921. PubMed ID: 7917511. An alternative view of the Th1/Th2 **switch** hypothesis in HIV infection. **Romagnani S**; Maggi E; Del Prete G. (Division of Allergology and Clinical Immunology, Istituto di Clinica Medica III, University of Florence, Italy.) AIDS research and human retroviruses, (1994 May) 10 (5) iii-ix. Ref: 49. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB A theory that seeks to explain what induces the relentless progression of HIV-infected subjects to AIDS has received considerable attention. This theory holds that HIV infection results in a Th1/Th2 **switch**. However, analysis of constitutive cytokine mRNA expression in lymphoid tissues from HIV-infected individuals did not confirm an in vivo Th1/Th2 **switch**. Moreover, data available at the level of in vitro-stimulated peripheral blood mononuclear cells or cloned T cells do not provide clear evidence for a definite **switch** to the Th2 responses in any HIV-infected subject and in any phase of HIV infection. At most, currently available data on the profile of cytokines released in response to in vitro stimulation suggest a Th1-to-Th0 shift in a proportion of memory CD4+ T cells. On the other hand, experiments of in vitro infection with HIV of already established CD4+ T cell clones indicated that Th2 and Th0 cells support HIV replication better than Th1 cells, suggesting that early destruction of Th2 cells by direct or indirect HIV-mediated cell killing may occur. Finally, in some HIV-infected individuals with low CD4+ T cell counts, a prevalence of CD8+ T cells producing type 2 cytokines was found in both peripheral blood and skin. Thus, although the induction of a general Th2 state in HIV infection is not proven, enhanced production of type 2 cytokines may occur in a proportion of HIV-infected individuals and play some role in the pathogenesis of the disease.

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(FILE 'HOME' ENTERED AT 20:24:11 ON 04 MAR 2004)

FILE 'USPATFULL' ENTERED AT 20:24:31 ON 04 MAR 2004
E MARCHALONIS JOHN J/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 20:28:49 ON 04 MAR 2004
E MARCHALONIS J J/IN
L2 5 S E2 OR E3

FILE 'MEDLINE' ENTERED AT 20:31:41 ON 04 MAR 2004
E MARCHALONIS J J/AU
L3 256 S E2-E5

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L4             75 S L3 AND (TCR OR T CELL RECEPTOR)
L5              4 S L4 AND (TH1 OR TH2 OR T HELPER OR TH1/TH2)
L6              0 S L4 AND (TH1 (W) TH2)

     FILE 'USPATFULL' ENTERED AT 20:41:14 ON 04 MAR 2004
L7           9668 S (TCR OR T-CELL RECEPTOR)
L8           7692 S L7 AND (PEPTIDE? OR POLYPEPTIDE?)
L9            816 S L8 AND (V BETA)
L10           123 S L9 AND (CDR1 OR COMPLEMENTAR? DETERMIN? REGION)
L11            39 S L10 AND (TH1 OR TH2 OR T HELPER 1 OR T HELPER 2)
L12            38 S L11 NOT L1

     FILE 'MEDLINE' ENTERED AT 20:45:51 ON 04 MAR 2004
L13         24107 S (T CELL RECEPTOR OR TCR)
L14          1326 S L13 AND (TH1 OR TH2 OR T-HELPER 1 OR T-HELPER 2)
L15            18 S L14 AND (ALTERED PEPTIDE LIGANDS)
                  E EVAVOLD B D/AU
L16            33 S E2-E4
                  E MADRENAS J/AU
L17            65 S E3 OR E4
L18            28 S L17 AND (TCR OR T-CELL RECEPTOR)
L19           229 S L14 AND (AUTOIMMUN? OR IMMUNE DYSFUNCTION OR CYTOKINE DYSFUNC
L20            65 S L19 AND (VACCIN? OR IMMUNIZ?)
L21           234 S L13 AND (TCR PEPTIDE? OR T-CELL RECEPTOR PEPTIDE? OR T-CELL R
L22            92 S L21 AND AUTOIMMUN?
                  E GRAZIOSI C/AU
L23            33 S E3
                  E ROMAGNANI S/AU
L24            12 S E4
                  E ROMAGNANI S/AU
L25           301 S E3
L26             6 S L25 AND SWITCH

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 21:53:30 ON 04 MAR 2004
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of more cytokines to said mammal.

37. The method of claim 33 or 35, further comprising contacting said sample or said T cells with one or more cytokines, wherein said contacting alters the ratio of **Th1**/**Th2**/immune deviation response by said contacted T cells

38. The method of claim 33 or 35, wherein said method is used in the treatment or prevention of an autoimmune disease, viral infection, bacterial infection, parasitic infection, infection by a eukaryotic pathogen, allergy, asthma, inflammatory condition, graft versus host disease, graft rejection, immunodeficiency disease, spontaneous abortion, pregnancy, or cancer in said mammal.

39. A method of purifying a subpopulation of T cells from a sample, said method comprising contacting said sample with an antibody or a combination of antibodies that preferentially binds a CDR3-loop or an α-β junction of a **TCR**; or an antibody that preferentially binds or modulates the expansion or activation of at least one T cell subpopulation selected from the group of NK T cells, CD1d-reactive T cells, and JαQ+ T cells.

40. The method of claim 39, further comprising contacting said sample with an anti-Vα24, CD4, CD8, CD56, CD161, or **V**β11 antibody.

41. The method of claim 39, wherein said antibody is covalently linked to a fluorescent label, wherein said complex is isolated based on the fluorescence signal of said complex.

42. The method of claim 39, wherein said antibody is covalently linked to a magnetic label, wherein said complex is isolated based on the magnetism of said complex.

L12 ANSWER 32 OF 38 USPATFULL on STN
2002:227648 Methods for treating inflammation.
Stern, David M., Great Neck, NY, UNITED STATES
Herold, Kevan, Scarsdale, NY, UNITED STATES
Yan, Shi Du, Tenafly, NJ, UNITED STATES
Schmidt, Ann Marie, Franklin Lakes, NJ, UNITED STATES
Lamster, Ira, Wycoff, NJ, UNITED STATES
US 2002122799 A1 20020905
APPLICATION: US 2001-872185 A1 20010601 (9)
PRIORITY: WO 1999-US23303 19991006
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a method for treating inflammation in a subject which comprises administering to the subject soluble receptor for advanced glycation endproduct (sRAGE) in an amount effective to inhibit binding of advanced glycation endproducts (AGEs) to RAGE thereby treating inflammation in the subject. The present invention also provides for a method for treating inflammation in a subject which comprises administering to the subject an agent in an amount effective to inhibit the interaction between receptor for advanced glycation endproduct (RAGE) and its ligand thereby treating inflammation in the subject.
CLM What is claimed is:
1. A method for treating inflammation in a subject which comprises administering to the subject soluble receptor for advanced glycation end product (sRAGE) (SEQ ID NO: 1) in an amount effective to treat inflammation in the subject.

2. A method for treating inflammation in a subject which comprises administering to the subject a **polypeptide** consisting essentially of the V-domain (SEQ ID NO: 2) of receptor for advanced glycation end product (RAGE) in an amount effective to treat inflammation in the

subject.

3. A method for treating inflammation in a subject which comprises administering to the subject an agent in an amount which inhibits the interaction between receptor for advanced glycation end product (RAGE) and its ligand thereby treating inflammation in the subject.

4. The method of claim 3, wherein the agent comprises a **polypeptide**, a peptidomimetic, an organic molecule, a carbohydrate, a lipid, an antibody or a nucleic acid.

5. The method of claim 4, wherein the **polypeptide** comprises an advanced glycation end product **polypeptide** or a portion thereof, a receptor for an advanced glycation end product **polypeptide** or a portion thereof, a soluble receptor for advanced glycation end product **polypeptide** or a portion thereof.

6. The method of claim 4, wherein the antibody comprises an anti-RAGE antibody or an anti-RAGE $F(ab')_2$ fragment.

7. The method of any one of claims 1 to 3, wherein the subject is a mammal.

8. The method of claim 7, wherein the mammal is a human.

9. The method of any one of claims 1 to 3, wherein the administration comprises intralesional, intraperitoneal, intramuscular or intravenous injection; infusion; liposome-mediated delivery; topical, nasal, oral, anal, ocular or otic delivery.

10. The method of claim 3, wherein the agent is administered daily.

11. The method of any one of claims 1 to 3, wherein the amount comprises a dose of from about 200 ng/day/kg body weight to about 200,000 ng/day/kg body weight.

12. The method of any one of claims 1 to 3, wherein the inflammation is associated with a wound in the subject.

13. The method of any one of claims 1 to 3, wherein the inflammation is associated with periodontal disease in the subject.

14. The method of any one of claims 1 to 2, wherein the inflammation is associated with an autoimmune disease in the subject.

15. The method of claim 14, wherein the autoimmune disease is multiple sclerosis or autoimmune encepthalitis.

16. The method of any one of claims 1 to 3, wherein the inflammation is associated with delayed-type hypersensitivity of a subject.

17. The method of any one of claims 1 to 3, wherein the inflammation is associated with arthritis in a subject.

18. The method of claim 17, wherein the arthritis comprises collagen-induced arthritis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, arthritis due to Behchet's Syndrome, arthritis due to Sjogren's Syndrome, or arthritis induced by lupus.

19. The method of any one of claims 1 to 3, wherein the inflammation is due to colitis in the subject.

20. The method of claim 19, wherein the colitis is ulcerative colitis.

21. The method of claim 19, wherein the colitis is due to Crohn's disease.

22. The method of any one of claims 1 to 3, wherein the subject is suffering from an allergy.

23. The method of any one of claims 1 to 3, wherein the subject is suffering from asthma.

24. The method of any one of claims 1 to 3, wherein the subject is suffering from diabetes.

25. The method of claim 23, wherein the asthma is allergic asthma.

L12 ANSWER 33 OF 38 USPATFULL on STN
2002:95358 Methods for treatment of multiple sclerosis using **peptide** analogs of human myelin basic protein.
Gaur, Amitabh, San Diego, CA, United States
Conlon, Paul, Solana Beach, CA, United States
Ling, Nicholas C., San Diego, CA, United States
Staehelin, Theophil, Arlesheim, SWITZERLAND
Crowe, Paul D., Encinitas, CA, United States
Neurocrine Biosciences, Inc., San Diego, CA, United States (U.S. corporation)Novartis, AG, Basel, SWITZERLAND (non-U.S. corporation)
US 6379670 B1 20020430
APPLICATION: US 1999-378244 19990819 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed toward **peptide** analogs of human myelin basic protein. The **peptide** analog is at least seven amino acids long and derived from residues 83 to 99 of human myelin basic protein. The analogs are altered from the native sequence at least at positions 91, 95, or 97. Additional alterations may be made at other positions. Pharmaceutical compositions containing these **peptide** analogs are provided. The **peptide** analogs are useful for treating multiple sclerosis.
CLM What is claimed is:
1. A method for inducing a **Th2** immune response to myelin basic protein or a **peptide** analog thereof in a patient, comprising: administering to a patient a pharmaceutical composition comprising a **peptide** analog consisting of the sequence D-Ala-Lys-Pro-Val-Val-His-Leu-Phe-Ala-Asn-Ile-Val-Thr-Pro-Arg-Thr-Pro (SEQ ID NO:7).

L12 ANSWER 34 OF 38 USPATFULL on STN
2001:178818 **T-cell receptor** Vβ-Dβ-Jβ sequence and methods for its detection.
Zhang, Jingwu Z., Missouri City, TX, United States
Baylor College of Medicine, Houston, TX, United States (U.S. corporation)
US 6303314 B1 20011016
APPLICATION: US 2000-507819 20000222 (9)
PRIORITY: US 1999-121311P 19990223 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB In one embodiment, the present invention is directed to a first oligonucleotide comprising the sequence of or derived from 5'-CTAGGGCGGGCGGGACTCACCTAC-3' or the nucleic acid sequence complementary thereto. The first oligonucleotide can be used with a nucleic acid of between 15 and 30 nucleotides that does not comprise the sequence of the first oligonucleotide and is found in the region from Vβ to Jβ of the Vβ13.1 gene in Vβ13.1 T cells, wherein the sequences of the oligonucleotide and the nucleic acid are not found on the same strand of the Vβ13.1 gene pair, to amplify a portion of the Vβ13.1 gene. Alternatively, the first oligonucleotide can be used with a labeling moiety in methods of detecting a LGRAGLTY motif found in T cell receptors of Vβ13.1